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Synthesis and Characterisation of a Mesocyclic Tripodal Triamine Ligand

Andrew D. Ure, Isabel Abánades Lázaro, Michelle Cotter, and Aidan R. McDonald*

Abstract: Meso- and macrocyclic polydentate amine ligands have been widely explored in oxidation catalysis and for the stabilization of unstable metal-superoxide, -peroxide, and -oxo intermediates. Herein we report on the design and synthesis of a novel mesocyclic, tripodal, triamine ligand that we believe will be an excellent addition to this field. We explored a number of synthetic procedures towards the mesocyclic asymmetric tetraalkylated ligand 1. We expect that 1 will bind metals in a facially capping manner, yielding complexes that display pseudo-tetrahedral geometry, potentially providing access to unprecedented late transition metal-oxo complexes (metal = Co, Ni, Cu). We describe the preparation of a library of mesocyclic polyamine synthons (8, 16, 17, 18, 19) that are precursors in the synthesis of 1. These synthons will be used to tailor the electronic properties of metal complexes of 1 and derivatives thereof. The X-ray crystal structures of 19 and mono- and di-protonated forms of 1b show that the triamine crystallises in a boat-chair conformation which is undesirable for metal coordination. However, solution 1H NMR studies show that in solution both 19 and the tetraalkylated derivative 1b are remarkably flexible. 1b reacted with [CuI(NCCH3)4](OTf) yielding a 1:1 copper(I) complex [Cu1(NCCH3)1b]+.

Introduction

Iron and copper containing metalloenzymes perform a variety of oxidative conversions of inert hydrocarbon substrates.1-5 These enzymes are capable of performing otherwise difficult oxidation reactions under ambient conditions. Terminal metal-oxo intermediates are often postulated as the reactive intermediates in these reactions. For example, in the cytochromes P450, Compound I (an FeIV=O species) performs hydrogen atom abstraction (HAA) of inert substrates.6 The di-copper enzyme particulate methane monooxygenase (pMMO) is capable of HAA from the strong C-H bond in methane (bond dissociation energy (BDE) = 104 kcal mol17), ultimately yielding methanol.8 The HAA reagent in pMMO is likely a bis-μ-oxo dicopper(III) (CuIII–O–CuIII) or a terminal CuIII=O species.9 These impressive HAA reactivities have driven synthetic chemists to develop bio-mimetic terminal metal-oxo complexes that can replicate this chemistry. While a plethora of well-characterised synthetic FeIV=O complexes has been reported,10-13 there remains no examples of CuIII=O and other terminal late transition metal-oxo (Co, Ni) complexes, although our group and others are making progress towards such species.14-17

A reason for the dearth in late transition metal-oxo complexes is that in certain geometries, d-electrons destabilise the metal-oxo interaction, preventing the isolation of metal-oxo’s of later transition metals.15, 17-19 Nocera postulated that late transition metal-oxo’s could be stabilised in complexes displaying low coordination numbers.20-24 Based on this postulate, we believe that late transition metal-oxo complexes could be accessible using ancillary ligands that enforce a pseudo-tetrahedral geometry. We therefore set out to design and synthesise ligands and complexes that display such a pseudo-tetrahedral geometry in order to prepare late transition metal-oxo complexes (Figure 1).

In our ligand design considerations we decided that the ligand must be tripodal and facially capping, so as to enforce a pseudo-tetrahedral coordination environment. Furthermore, the ligand should contain strong σ-donor atoms in order to stabilise the high oxidation state of the metal centre in metal-oxo complexes. Meso- and macro-cyclic, peralkylated amine

![Figure 1](image-url)

Figure 1 – Left: Target compound 1, Right: a generic pseudo-tetrahedral metal-oxo.
ligands have been used to great success in stabilizing early transition metal-oxo complexes \( \text{metal} = \text{Mn, Fe}^{11-13, 25-27} \) and late transition metal-superoxide and -peroxide complexes.\(^{28-36}\) Meso- and macro-cyclic frameworks add further stability to complexes bearing these ligands, because of the macrocyclic effect.\(^{37, 38}\) Based on these considerations, we set-out to prepare mesocyclic ligand 1 (Figure 1).

1 is a close analogue of the tripodal acyclic ligand 1,1,1-tris(aminomethyl)ethane (TAME, Figure 2). Due to the lack of steric bulk in TAME, 2:1 complexes are often formed. Increasing the steric bulk via \(N\)-alkylation to give 1,1,1-tris(N,N-dimethylenamino)methylethane (Me\(_t\) TAME, Figure 2) resulted in the ligand switching from binding to metals in a tridentate fashion, to a bidentate binding mode, with one of the nitrogens remaining unbound.\(^{39}\) Similarly, the more bulky guanidine derivative of TAME, 1,1,1-tris(2N,1,1,3,3-tetramethylguanidino)methylethane (guanTAME, Figure 2) has been shown to exhibit variable denticity.\(^{40, 41}\) We postulate that the mesocyclic nature of 1 and the steric bulk around the putative metal-binding site will ensure 1 would bind in a tridentate fashion yielding 1:1 complexes.\(^{38}\)

1 is also a close analogue of the 1,5-diazacyclooctane (DACO, Figure 2) family of ligands.\(^{38, 42, 43}\) DACO ligands tend to bind to the metal with the DACO framework displaying a boat-chair configuration.\(^{44}\) These observations are important because we require that 1 binds to metals yielding a chair-boat configuration to ensure pseudo-tetrahedral geometry. Several derivatives of DACO have been developed, exclusively through \(N\)-alkylation (Figure 2).\(^{33-36, 45-53}\) In general, these ligands yield square planar complexes. Overall, while many \(N\)-alkylated derivatives of DACO exist, few tetrahedral complexes employing DACO have been reported, and all are lacking the high degree of steric bulk that we require. We envisioned that introducing a third donor atom to DACO at the 3-position of the DACO ring, rather than through \(N\)-alkylation, would present several benefits. Firstly, introduction of ligating functionalities at the 3-position would ensure a facially capping ligand (and a pseudo-tetrahedral complex), whereas \(N\)-alkylated derivatives of DACO are mainly meridional binders. Secondly, organic functionalities can be readily introduced through \(N\)-alkylation in 1, allowing us to easily modulate the electronic and steric properties of the ligand. Herein, we describe our efforts towards synthesizing the novel ligand 1 and derivatives thereof.

**Results and Discussion**

We identified triol 1,1,1-tris(hydroxymethyl)ethane (2, Scheme 1), as a useful starting point for the preparation of 1. In order to prepare the asymmetric molecule 1, we attempted to address a single arm of the tri-substituted neo-pentyl framework, leaving the other two arms to be the basis of the 8-membered mesocycle. To this end we attempted to selectively address one of the hydroxyl groups of 2 while protecting the other two hydroxyl groups. We prepared the bis-protected triol (1,3-dioxane, 3) according to a previously published procedure.\(^{54}\) The remaining hydroxyl group in 3 was then activated through reaction with one equivalent of tosyl chloride (tosyl (Ts) = 4-toluenesulphonyl) in pyridine to give the corresponding tosylate 4.\(^{55}\) The azide, 5, was then prepared through nucleophilic substitution of the tosylate with sodium azide according to the procedure reported by Liu.\(^{56}\) We subsequently pursued two avenues towards the selective derivatisation of azide 5 (Scheme 2), but neither provided us with an efficient or facile route towards 1.

In the first of these routes, we utilised the azide moiety as a masked amine. 5 was refluxed with aqueous HCl in tetrahydrofuran (THF) for 30 minutes to cleave the dioxane protecting group.\(^{56}\) The resulting diol (6) was then immediately reacted with 2.2 equivalents of tosyl chloride in the presence of aqueous sodium hydroxide in THF to give the bis-tosylate 7 in a 64 % yield. Cyclic polyanimes, including DACO, are readily synthesised via the Richman-Atkins method of cyclisation.\(^{57, 58}\) In general, this involves the reaction of a di-tosylated diol (such as 7) with a deprotonated bis-tosylamide to facilitate cyclisation. In order to perform the cyclisation reaction of ditosylates like 7, we prepared the activated diamine \(N,N'-(\text{propane-1,3-diy})\text{bis}-\text{tosylamide} \) (12) by reacting 1,3-diaminopropane (11) with tosyl chloride according to a reported procedure (Scheme 3a).\(^{52}\) 12 was then deprotonated using NaH and subsequently stirred with 7, without work-up,
at 145 °C in anhydrous dimethylformamide (DMF). Analysis of the post-reaction mixture indicated none of the desired cycle had formed. We attributed this to the organic azide being unstable under the high-temperature reaction conditions. The azide group may act as a leaving group under such forcing conditions.

As a result of this negative outcome, we revisited the protected azide, 5. Rather than cleaving the dioxane group we proceeded to reduce the azide moiety. This was achieved by reacting 5 with 10% wt of 5% Pd/C in the presence of ammonium formate in methanol to give the primary amine 9 in a 50% yield. We then attempted to methylate the primary amine in 9 using 2 equivalents of methyl iodide. However, ESI-MS revealed the formation of a statistical distribution of all of the possible methylation products (secondary, tertiary and quaternary), rather than a majority of the tertiary amine. These products were not separable using column chromatography. We then attempted the methylation of 9 under Eschweiler-Clarke conditions. 9 was refluxed for 6 hours in an excess of formic acid and formaldehyde. After work up, the 1H NMR showed the disappearance of the two characteristic dioxane methyl peaks at 1.41 and 1.45 ppm, indicating that the dioxane protecting group had been cleaved under these reaction conditions, giving no indication of the formation of the desired product 10.

Given these unexpected setbacks, we decided that rather than selectively address individual arms of the triol precursor 1, we would perform cyclisation reactions on activated derivatives of triol 2, without protecting any of the hydroxyl functionalities. We anticipated difficulties with this approach because of the potential formation of oligomers and polymers in the Richman-Atkins cyclisation reaction, however it was a necessary approach. 2 was activated through its reaction with tosyl chloride (4 equiv.) in pyridine (Scheme 3b) yielding the tris-tosylate 13 in 83% yield. While 13 can be isolated simply by precipitation after addition of ice-water followed by filtration, we found that the work-up reported by Lindhorst and co-workers, in which the product was extracted with ethyl acetate and dried over magnesium sulphate, gave an anhydrous product. This anhydrous product was better suited to the cyclisation step discussed below (Scheme 4), because it must be performed under strictly anhydrous conditions.

Importantly, we found that the tris-tosylate 13 was easily converted to the tris-bromide 14 in 76% yield by reaction between 13 and NaBr in diethylene glycol heated to 145 °C. Using this method 14 can be used without further purification, unlike the previously reported reaction of the tris-benzenesulphonate analogue of 13 with NaBr, which we found required the product be purified by distillation. While there are several reports detailing the synthesis of 14 directly from the reaction between 2 and PBr3, we have found them difficult to reproduce, and therefore prefer this two-step procedure for the preparation of 14. These two activated tripodal neopentane precursors provide two useful synthons towards the preparation of 1.

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We reacted the bis-tosylamide, 12, with the activated triols 13 and 14 under conditions outlined by Richman and Atkins (Scheme 4).\(^5\) The disodium salt of 12 (15) was generated in situ by reacting 12 (0.1 M, 100 mL) with two equivalents of sodium hydride in anhydrous DMF. After hydrogen evolution had ceased (gas bubbles were no longer observed), the reaction mixture was heated at 100 °C under argon for one hour. A 0.2 M solution (50 mL) of an activated triol (13 or 14) in anhydrous DMF was then added dropwise. The resulting reaction mixture was heated at 145 °C under argon flow for at least 24 h. This yielded the desired cyclised products 16a and 16b. 16a and 16b were characterised using \(^1\)H and \(^13\)C NMR spectroscopies and mass spectrometry. The \(^1\)H NMR spectra displayed resonances typical of a mesoyclic aliphatic hydrocarbon, confirming cyclisation occurred. Additionally, single crystals of 16b suitable for x-ray diffraction were grown by slow evaporation of a solution of 16b in CHCl\(_3\) (Figure 3b, Table S1). Heating at temperatures lower than 145 °C resulted in no cyclised product formation. Such forcing reaction conditions were required because of the neopentyl backbone, in which the bulky vicinal substituents sterically shield the carbon atom that the activated amine groups are attacking.\(^5\) Furthermore, the yield of the desired cyclised product was significantly higher if tris-bromide 14 was used (16b obtained in 48% yield). The yield of 16a from cyclisation using activated triol 13 was 10%. Additionally, while Richman and Atkins report that reaction solution concentrations for their cyclisations must be finely tuned to prevent oligomer/polymer formation,\(^5\) we have found that the poor kinetics of this cyclisation reaction acts as an effective dilution.

After preparing the 1,5-diazacyclooctane mesocycles 16a and 16b, we then sought to introduce an amine functionality onto the remaining arm. We have adopted two approaches to aminating 16a and 16b (Scheme 4). In the first approach, we reacted the 1,5-diazacyclooctane mesocycles 16a and 16b with sodium azide to yield the azide 8. Formation of 8 was confirmed using NMR spectroscopy and Mass spectrometry. In the Fourier transform infra-red (FT-IR) spectrum of 8, a strong band at 2103 cm\(^{-1}\), which we assign as an N\(_2\) vibrational mode, was observed. The azide group in 8 was then reduced, using 5% Pd/C and ammonium formate in methanol, to give the amine 17 as confirmed by NMR and ESI-MS. The disappearance of the FT-IR band at 2103 cm\(^{-1}\) and the appearance of the characteristic amine symmetric and asymmetric stretching frequencies at 3309 and 3151 cm\(^{-1}\) was noted, confirming reduction of the azide moiety in 8 to an amine in 17. The N-tosyl protecting groups in 17 were then cleaved by heating 17 in 33% HBr/acetic acid (Scheme 4). No aromatic peaks were observed in the \(^1\)H NMR of the triamine product 19, which was purified as the tris-hydrogen bromide salt, indicating complete N-tosyl deprotection and isolation of the desired triamine product.

![Scheme 4 – Cyclisation reactions and derivatisation of cyclised products.](image-url)

We sought an alternative synthetic route to 19, because the azide reduction described above gave inconsistent yields. To this end, we reacted 16b with sodium tosylamide at 145 °C in anhydrous DMF to give the tosylamide 18 (Scheme 4). The formation of 18 was confirmed by \(^1\)H NMR and \(^13\)C NMR spectroscopy, which showed the aromatic and aliphatic bromine and hydrogen atoms have been omitted for clarity. a) ORTEP plot of the X-ray crystal structure of 19•3HBr at 50% probability. b) ORTEP plot of the X-ray crystal structure of 16b at 50% probability. N-Tosyl groups and hydrogen atoms have been omitted for clarity.

![Figure 4 – a) \(^1\)H NOE Spectrum of the 19 irradiated at 1.72 ppm; b) \(^1\)H Spectrum of the 19; c) \(^1\)H Spectrum of 1b; d) ROESY Spectrum of 1b irradiated at 1.63 ppm.](image-url)
resonances expected after the inclusion of the third tosylamide functionality. ESI-MS also confirmed the formation of 18 (m/z = 620.1931 for C₂₀H₂₇N₃O₆S₂; expected m/z = 620.1923). All N-tosyl groups were then cleaved by treatment with 33% HBr/acetic acid to give the triammonium salt 19•3HBr in a 10% yield. The yield of the deprotection step when conc. H₂SO₄ was used instead of HBr/acetic acid was significantly higher at 50%. This corresponds to an overall yield of 20%, much improved on the overall yield of 4% when HBr/acetic acid was used for deprotection.

Single crystals of 19•3HBr suitable for X-ray diffraction were obtained by diffusing ethanol into a solution of 19•3HBr in water. This was an important achievement as we wanted to understand the structure and structural flexibility of our mesocyclic ligands. Crystal data and refinement parameters are shown in Table S1. Analysis of the crystal structure of 19•3HBr (Figure 3a) showed that the DACO ring in 19•3HBr displayed a boat-chair conformation. All bond lengths were in agreement with those previously reported for diprotated DACO rings. Unusually, when compared to the other crystal structures we obtained (vide infra) and those previously reported in the literature for a diprotated DACO moiety, the nitrogen lone pairs in 19•3HBr are located on opposite faces of the ring. This arrangement would disfavor complex formation. We reason that this occurs as it allows for the maximum separation of the two positively charged nitrogen atoms.

![Chemical structures](image)

Table 1 – Selected bond lengths and angles for the reported crystal structures.

<table>
<thead>
<tr>
<th></th>
<th>19•3HBr</th>
<th>16b</th>
<th>[1b•H][PF₆]</th>
<th>[1b•2H][OTf]₂</th>
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</thead>
<tbody>
<tr>
<td>Mean Cyclic C-C / Å</td>
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<td>1.532</td>
<td>1.531</td>
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<tr>
<td>Mean C-N1 / Å</td>
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<td>1.480</td>
<td>1.484</td>
<td>1.475</td>
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<tr>
<td>Mean C-N2 / Å</td>
<td>1.495</td>
<td>1.477</td>
<td>1.514</td>
<td>1.519</td>
</tr>
<tr>
<td>Mean C-N3 / Å</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N4-N8 Distance / Å</td>
<td>3.632(2)</td>
<td>2.8572(1)</td>
<td>2.6906(1)</td>
<td>2.8003(1)</td>
</tr>
<tr>
<td>C3-N1-C5 Fold Angle / °</td>
<td>N/A</td>
<td>115.369(2)</td>
<td>111.408(2)</td>
<td>113.450(3)</td>
</tr>
<tr>
<td>C7-N2-C9 Fold Angle / °</td>
<td>N/A</td>
<td>116.590(2)</td>
<td>111.466(2)</td>
<td>113.569(3)</td>
</tr>
</tbody>
</table>

In order to promote the formation of pseudo-tetrahedral complexes, we required that 1 displayed the ability to form an alternative boat-chair conformation analogous to that shown by 16b (Figure 3b), where the nitrogen atoms are primed to bind the metal in a pseudo-tetrahedral fashion. We therefore probed the solution behaviour of 19 further. ¹H NOE NMR studies on 19 (Figure 4, prepared by deprotonation of 19•3HBr with KOH) were performed. The NOE spectra, with irradiation of the multiplet at 1.70 ppm (corresponding to the central CH₂ of the propylene linker (CH₂−CH₂−CH₂), showed that this -CH₂- displayed through-space coupling to all other protons in the molecule. Of note is the through-space coupling to both the CH₃ group and CH₂NH₂ of the primary amine, indicating that the central CH₂ of the propylene linker can 'see' both faces of the mesocycle. This demonstrated that 19 retains a high degree of flexibility in solution and indicated that 1 would be sufficiently flexible to bind metals in the desired manner.

We attempted to methylate 19•3HBr to give the tetramethylated triamine product 1a under Eschweiler-Clarke conditions. 19•3HBr was refluxed in formic acid in the presence of an excess of formaldehyde. From this reaction we identified a mixture of products (at least 4) by ¹H NMR, none of which could be attributed to the desired peralkylated product, while suggesting that all of the starting material 19•3HBr had been consumed. We postulated that an intermediate imine that formed upon initial reaction between the amine groups in 19•3HBr and formaldehyde, was not fully reduced prior to a secondary reaction between the imine and one of the other adjacent amine groups of the triamine 19. This resulted in the formation of aminal containing cyclic amines rather than the desired permethylated product 1a. To overcome this we attempted several reductive aminations utilising more powerful reducing agents. 19•3HBr was refluxed with an excess of formaldehyde and acetic acid in the presence of stronger reductants (NaBH₄, KBH₄, or zinc). Unfortunately similar ¹H NMR spectra, indicative of aminal formation, were obtained in all cases. Unfortunately, permethylation of 19•3HBr was also not possible using methyl tosylate or iodomethane as we consistently obtained over-alkylated products, in the presence of the desired product 1a (according to ESI-MS and ¹H NMR), that were not separable by column chromatography.

Fortunately, however, we found that we were able to alkylate 19•3HBr using benzyl bromide. The reaction of 19•3HBr with exactly four equivalents of benzyl bromide in the presence of excess base (Na₂CO₃) gave the tetra-alkylated product 1b.
Further, a multiplet at 7.4 ppm was observed, which corresponds to the phenyl groups of the benzylic functionalities. A peak in the ESI-MS was observed at m/z = 518.3534 (expected m/z = 518.3535 for C_{16}H_{14}N_{2}), confirming the identity of 1b. The reaction between 19•3HBr and benzylic bromide did not yield over-alkylated quaternised amine products, whereas the reaction between 19•3HBr and iodomethane did. We ascribe this difference in reactivity to the steric bulk of the benzyl functionality retarding the rate of the quaternization reaction compared to methyl functionalities. This provides a strong indication that the benzyl functionalised ligand 1b will have a sterically protected metal binding pocket.

Similar to 19•3HBr we assessed the solution flexibility of 1b (Figure 4) with $^1$H Rotating-frame Overhauser Effect Spectroscopy (ROESY) NMR. Irradiation of the central CH$_2$ of the propylene linker CH$_2$ of the mesocycle at 1.63 ppm showed through-space coupling to all of the other protons within the DACO ring, as well as the benzyl CH$_2$ groups and, importantly, the exo-cyclic CH$_3$ and CH$_2$ groups. This demonstrated that although we have alkylated all amine groups in 1b, the molecule retains structural flexibility, and should bind metals in the desired pseudo-tetrahedral geometry.

Similarly, single crystals of [1b•2H][OTf]$_2$ (Figure 5b) were obtained after layering of a wet CH$_3$CN solution of 1b and Zn(OTf)$_2$ with Et$_2$O. The crystal structures shown in Figure 5 unambiguously demonstrate that the cyclic amine was protonated before the acyclic amine, as would be expected based on their reported higher basicity. Selected bond lengths and angles for these structures, as well as those in Figure 3, are shown in Table 1.

The structure of [1b•H]PF$_6$ consists of a discrete 1b•H$^+$ cation and a PF$_6$ anion. The DACO ring adopts a boat/chair conformation, and has a C-N-C fold angle of 111°. The average cyclic C-C bond length remains similar to those found for 19•3HBr and 16b, (~1.5 Å). Protonation of N2 results in a larger mean C-N2 bond length (1.51 Å) when compared to the mean C-N1 bond length (1.48 Å), which is in agreement with the C-N bond lengths discussed above for 19•3HBr and 16b. The N1-N2 distance for [1b•H]PF$_6$ is 2.69 Å, comparable to that measured for 16b and significantly shorter than that measured for 19•3HBr suggesting that monoprotonation of the DACO ring allows for the nitrogen atoms to be in closer proximity. The structure of [1b•2H][OTf]$_2$ consists of a discrete 1b•2H$^+$ cation and two triflate anions. After protonation of N2 and N3 (rather than N1), the structure retains the same boat/chair conformation as in [1b•H]PF$_6$. In the structures of both [1b•H]PF$_6$ and [1b•2H][OTf]$_2$, the C-N-C fold angle is comparable to both previously reported protonated DACO moieties\textsuperscript{58, 65, 67, 68} as well as metal complexes containing the DACO moiety.\textsuperscript{35} Furthermore, the bond lengths and angles were found to be in the region of those previously reported. This suggests that alkylation of the DACO ring at the C2, N1 and N2 positions should not hinder complex formation.

The $^1$H NMR of the crystals of [1b•H]PF$_6$ and [1b•2H][OTf]$_2$ are shown in Figure 6 and were assigned in conjunction with the corresponding heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond correlation HMBC spectra (See supporting information, Figures S30-35). The $^1$H NMR of the freebase 1b and of [1b•H]PF$_6$ are shown in Figure 6a and 6b respectively. The spectra show that upon protonation at N2 (Figure 6b), the apparent singlet at 3.59 ppm arising from H$_{6/6'}$ in 1b resolves into the pair of doublets, at 3.84 and 3.65 ppm in [1b•H]PF$_6$. The coupling constant (~13 Hz) indicates that these doublets are a result of geminal coupling and no $^1$J N-H coupling is observed. The difference between these chemical shifts (~0.2 ppm) is a result of the relative axial/equatorial arrangement of these diastereotopic protons, arising from a change in local magnetic anisotropy brought about by protonation. An equivalent resolution of signals is observed after protonation at N3 (Figure 6c), H$_{7/7'}$ are resolved into a pair of signals at 4.60 and 4.32 ppm. The doublet at 4.60 has a coupling constant (~14 Hz) indicative of geminal coupling only, whereas the multiplet at 4.32 is split

Crystal Structures of both the monoprotonated and diprotonated congeners of 1b were obtained (Figure 5, Table S1). Serendipitously, single crystals of [1b•H]PF$_6$ (Figure 5a) precipitated after layering a reaction mixture of 1b, CuCl$_2$ and KPF$_6$ in wet acetonitrile (CH$_3$CN) with diethylether (Et$_2$O).
Encouragingly, no 2:1 (ligand:metal) species were observed in the ESI-MS spectra. These observations suggest that 1b binds the metal centre as a tripod yielding a four-coordinate complex. Unfortunately, work-up of this reaction mixture did not yield the desired complex. Consequently, the same reaction was repeated utilising dichloromethane (DCM) as the reaction solvent (CH$_3$CN was eliminated from the reaction as we suspect the complex is unstable in CH$_3$CN). Figure 8 shows the $^1$H NMR spectrum of the yellow solid obtained from the DCM reaction mixture. The signal assignments shown in Figure 8 were made in combination with HSQC spectra (Figure S38). The splitting of the diastereotopic signals resembles that observed after protonation of 1b, however, the new material displayed resonances distinct from those of 1b, [1b$\cdot$H$\cdot$PF$_6$] and [1b$\cdot$2H$\cdot$OTf]$_2$, indicating complexation of Cu$^{II}$ by 1b had occurred. Notably, a resonance at 2.42 (corresponding to 3 protons) was observed. We assigned this to a coordinated CH$_3$CN ligand (uncoordinated CH$_3$CN = 2.01 ppm). This assignment was confirmed by the presence of a high-field signal at 2.9 ppm in the $^{13}$C NMR, typical of a nitrile methyl group. Integration of the resonances in Figure 8 showed a 1:1 ratio of 1b to CH$_3$CN, and thus a coordination number of four. This is further corroborated by our ESI-MS data that indicated the formation of [Cu$^{II}$\{NCCH$_3$\}_3(1b)]$^+$ complexes containing the DACO moiety tend to form four or five coordinate complexes (vide supra) and six coordinate complexes are unprecedented. Furthermore, Cu(I) complexes prefer to sit in tetrahedral geometry. We are therefore confident in our assignment of this spectrum as a pseudo-tetrahedral species [Cu$^{II}$\{NCCH$_3$\}_3(1b)]$^+$.

**Conclusion**

We have outlined several synthetic routes towards our target ligand 1, a novel, mesocyclic, tripodal, triamine ligand. Our modular approach to the synthesis of 1 has provided us with a library of synthons that will allow us to tune the reactivity of metal complexes of 1. Importantly, we have developed and optimised the synthesis of the mesocyclic fragment in 1.
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Present work in our lab is focused on preparing further molecular sieves and basic alumina. We have also been able to prepare [Cu(NCCH3)(1b)] demonstrating the potential of 1b to form pseudo-tetrahedral metal complexes. Present work in our lab is focussed on preparing further derivatives of ligand 1, and preparing metal-oxo species derived from low-valent copper and nickel complexes of 1b.

Experimental Details

All reagents and solvents were purchased from commercial sources and used as received, unless otherwise stated. All reactions with air-sensitive materials were conducted under an inert atmosphere using either standard Schlenk techniques or sources and used as received, unless otherwise stated. All reagents and solvents were purchased from commercial

**Synthesis of 3-(azidomethyl)-3-methyl-1,5-ditosyl-1,5-diazocane (8)**

16a (800 mg, 1.3 mmol) was dissolved in diethylene glycol (25 mL). Sodium azide (252 mg, 3.9 mmol) was added and the reaction mixture was stirred at 135 °C for 5 days. The reaction mixture was cooled and diluted with water (25 mL). The resulting emulsion was extracted with DCM (3 x 25 mL). The organic layer was collected and dried over MgSO₄ and the solvent removed in vacuo. The crude product was purified by column chromatography (EtOAc: Hexane: Triethylamine, 45:45:10) to give azide 8 (280 mg, 44%) as a white powder.

**Synthesis of 2,2,5-trimethyl-1,3-dioxan-5-yl)methanimine (9)**

Azide 5 (3.52 g, 19 mmol) and ammonium formate (4.87 g, 76 mmol) were added to degassed methanol (100 mL) and stirred until the ammonium formate completely dissolved. 5% Pd/C (365 mg, 10% wt) was then added and the reaction mixture stirred for 3 hours at room temperature. The reaction mixture was then filtered through a pad of Celite and the methanol removed in vacuo. The residue was taken up into distilled water (10 mL) and washed with Et₂O (3 x 20 mL). The aqueous layer was then basified with KOH (10 g) and extracted with CH₃CN (5 x 10 mL). The organic layer was collected and dried over MgSO₄. The solvent was removed in vacuo to give 9 (1.50 g, 50%) as a colourless oil.
was purified by column chromatography (EtOAc: Hexane: Triethylamine, 35:60:5) to give
cooling, the reaction mixture was diluted with deionised water (250 mL), mixed vigorously, then transferred to a separating funnel. The more dense oil
was removed
heated at 145 °C for 1 hour. A solution of 1,3-dibromo-2-(bromomethyl)-2-methylpropane 14 (3.8 g, 12.3 mmol) in anhydrous DMF (50 mL) was then added dropwise by cannula. The reaction mixture was heated at 145 °C for a further 24 hours. The DMF was removed by distillation and the residue was taken up into EtO (150 mL). The EtO solution was washed with water (3 x 50 mL) and brine (3 x 50 mL) and dried over MgSO4. The solvent was removed in vacuo. The crude product was purified by recrystallisation in the minimum amount of boiling methanol. The product was collected by vacuum filtration and washed with cold methanol (3 x 10 mL) to give 16b as an off white solid (3.1 g, 48%).

Synthesis of 1,3-dibromo-2-(bromomethyl)-2-methylpropane (14)

13 (46 g, 79 mmol) and NaBr (83 g, 790 mmol) were heated in diethylene glycol (250 mL) at 145 °C for 18 hours. After cooling, the reaction mixture was diluted with deionised water (250 mL), mixed vigorously, then transferred to a separating funnel. The more dense oil (14) was collected. The aqueous layer was washed with EtO (3 x 50 mL). The organic extracts were combined with the oil and dried over MgSO4. The solvent was removed in vacuo to give 14 (18.5 g, 76%) as a pale yellow oil.

Synthesis of (3-methyl-1,5-ditosyl-1,5-diazocan-3-yl)methanamine (17)

In a glove box, N,N’-(propane-1,3-diyl)bis-tosylate (16a) (3.80 g, 5.78 mmol) in anhydrous DMF (60 mL) was then added dropwise by cannula. The reaction mixture was then heated at 145 °C for a further 24 hours. The DMF was removed by distillation and the residue was taken up into CHCl3. The organic layer was washed with water (3 x 50 mL) and brine (3 x 50 mL) then dried over MgSO4. The solvent was removed in vacuo. The crude product was purified by column chromatography (EtOAc: Hexane: Triethylamine, 35:60:5) to give 16a (591 mg, 10%) as an off white crystalline solid.

1H NMR (600 MHz, CDCl3) δ = 1.14 (s, 3H), 1.92 (m, 2H), 2.44 (s, 6H), 2.45 (s, 3H), 3.11- 3.21 (m, 8H), 4.05 (s, 2H), 7.32 (d, J = 8.0, 4H), 7.36 (d, J = 8.1, 2H), 7.62 (d, J = 8.2, 4H), 7.84 (d, J = 8.3, 2H).

13C NMR (151 MHz, CDCl3) δ = 21.1, 21.6, 21.7, 21.8, 28.8, 39.8, 49.7, 53.2, 76.4, 127.5, 128.2, 130.0, 130.1, 132.7, 134.9, 143.9, 145.0.

ν max /cm⁻¹: 1156, 1174, 1307, 1336


Melting point: 86-88°C

Synthesis of 3-(bromomethyl)-3-methyl-1,5-ditosyl-1,5-diazocane (16b)

In a glove box, N,N’-(propane-1,3-diyl)bis-tosylate (12) (4.7 g, 12.3 mmol) was dissolved in anhydrous DMF (200 mL). NaH, as a 60% dispersion in mineral oil (0.985 g, 24.6 mmol) was added and the solution stirred until the evolution of hydrogen gas ceased. The reaction vessel was transferred to a Schlenk line and heated at 145 °C for 1 hour. A solution of 1,3-dibromo-2-(bromomethyl)-2-methylpropane 14 (3.8 g, 12.3 mmol) in anhydrous DMF (50 mL) was then added dropwise by cannula. The reaction mixture was heated at 145 °C for a further 24 hours. The DMF was removed by distillation and the residue was taken up into EtO (150 mL). The EtO solution was washed with water (3 x 50 mL) and brine (3 x 50 mL) and dried over MgSO4. The solvent was removed in vacuo. The crude product was purified by recrystallisation in the minimum amount of boiling methanol. The resulting white precipitate was collected by filtration and

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Organic solution of diffraction were grown by slow diffusion of ethanol into a off white solid (~10%). Crystals of filtration and washed with EtO (~1 mmol). The reaction mixture was heated under argon at 160 °C for 1 hour. The reaction mixture was cooled to 0°C in an ice-bath and ethanol (10 mL) followed by EtO (8 mL) was added dropwise. The reaction mixture was cooled in the freezer at -40°C overnight. The resulting white precipitate was collected by filtration onto a pad of celite. The precipitate and the celite were then transferred to a round-bottomed flask to which water (10 mL) and activated carbon were added. The mixture was refluxed for 1.5 hours. The insoluble materials were removed by filtration and the solvent was removed under reduced pressure. The resulting brown residue was taken up into 48% hydrobromic acid (1 mL) and to this solution ethanol (20 mL) was added dropwise. The resulting white precipitate, 19·3HBr (~50%) was collected by filtration and washed with cold EtO (5 mL).

General procedure for the generation of the Freebase 19.

19·3HBr was dissolved in the minimum amount of deionised water. NaOH (10 e.q) and toluene (~20 mL) were then added. The toluene solution was then heated under reflux with a Dean-Stark trap for 24 hours. After cooling, the any insoluble material was removed by filtration and the solvent removed under vacuum to give 19 as a colourless oil.

HRMS (m/z -ESI): Found: 518.3535. Melting point: 110-114°C

General Procedure for the Deprotection of N-Tosyl Protected Amines to give 19·3HBr Using 33% HBr in Acetic Acid and Phenol

A solution of 33% HBr in acetic acid (1 mL) was added to the protected amine (0.25 mmol.) and phenol (1 g). The reaction mixture was heated at 90 °C for 16 hours. The temperature was lowered to 60 °C and 33% HBr in acetic acid (1 mL) was added and the reaction mixture heated for a further 5 hours. The reaction mixture was cooled in the freezer at -40°C overnight. The resulting white precipitate was collected by filtration and washed with EtO (5 mL). To give 19·3HBr as an off white solid (~10%). Crystals of 19·3HBr suitable for X-ray diffraction were grown by slow diffusion of ethanol into a solution of 19·3HBr in water.

19·3HBr: 1H NMR (400 MHz, D2O) δ = 1.24 (s, 3H), 2.23 (m, 2H), 3.14 (s, 2H), 3.46 – 3.24 (m, 8H). 13C NMR (151 MHz, D2O) δ = 18.8, 19.2, 42.6, 43.8, 45.5, 47.5. HRMS (m/z -ESI): Found: 158.1695 (M+ + H). C29H33N3O5S3 predicted mass: 518.1652. Melting point: Decomposes at ~255°C.
NMR Data for [1b•2H][OTf]$_2$

$^1$H NMR (600 MHz, CDCl$_3$) $\delta = 0.15$ (5 H, 3H), 1.68-1.71 (m, 2H), 1.95-1.98 (m, 2H), 2.52 (d, $J = 14.5$ Hz, 2H), 2.42 (d, $J = 14.5$ Hz, 2H), 2.65-2.75 (m, 2H), 2.98-3.13 (m, 4H), 3.76 (d, $J = 13.0$ Hz, 2H), 3.82 (d, $J = 13.1$ Hz, 2H), 4.27-4.35 (m, 2H), 4.61 (d, $J = 12.6$ Hz, 2H), 7.23-7.69 (m, 20H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta =$ 18.9, 20.8, 35.4, 55.7, 56.1, 59.1, 63.2, 63.6, 129.2, 130.1, 130.2, 130.4, 131.4, 131.6, 133.6, 133.7.

Synthesis of [Cu(NCCH$_3$)$_3$(1b)][OTf] (21)

In a glovebox, 1b (0.079 g, 0.15 mmol) and [Cu(NCCH$_3$)$_3$][OTf] (0.063 g, 0.17 mmol) were stirred in anhydrous DCM (2 mL) for 10 minutes. The reaction mixture was then concentrated for 10 minutes. The reaction mixture was then concentrated under vacuum. Anhydrous CH$_2$N$_2$ (15 mL) was added resulting in a precipitate. The precipitate was collected by vacuum filtration and washed with anhydrous Et$_2$O (2 x 5 mL) to give [Cu(NCCH$_3$)$_3$(1b)][OTf] (0.045 g, 49%) as pale yellow solid. ESI-MS (m/z - ESi): Found: 619.0834 (M$^+$ + K). C$_{36}$H$_{43}$N$_3$Cu$^+$K predicted mass: 619.2390.

Air sensitive compound, no melting point determined.

Synthesis of [Cu(NCCH$_3$)$_3$(1b)][PF$_6$] (22)

In a glovebox, 1b (0.050 g, 0.09 mmol) and [Cu(NCCH$_3$)$_3$][PF$_6$] (0.040 g, 0.1 mmol) were stirred in anhydrous DCM (2 mL) for 10 minutes. Anhydrous Et$_2$O (15 mL) was added resulting in the formation of a pale yellow precipitate. The supernatant was decanted and the precipitate dissolved in the minimum amount of DCM. The resulting solution was then concentrated under anhydrous Et$_2$O and the precipitate recrystallized to give 1b as pale yellow needles (0.048 g, 65%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 0.17 (5 H, 3H), 1.84-1.98 (m, 2H), 2.04-2.11 (m, 4H), 2.33 (d, $J = 14.5$ Hz, 2H), 2.42 (s, 3H), 2.55-2.63 (m, 2H), 3.19 (d, $J = 12.3$ Hz, 2H), 3.43 (s, 4H), 3.50-3.63 (m, 2H), 3.96 (d, $J = 12.3$ Hz, 2H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta =$ 2.9, 23.8, 24.4, 30.9, 38.4, 59.2, 59.4, 61.7, 62.2, 67.1, 127.5, 128.4, 128.6, 129.3, 130.9, 131.6, 134.8, 139.3.

Acknowledgements

This publication has emanated from research supported in part by the European Union (FP7-333948) and a research grant from Science Foundation Ireland (SFI/12/RC/2278). We thank Dr. John O’Brien (NMR) and Dr. Brendan Twamley (XRD) for technical support. Dr. Brendan Twamley acknowledges PRTLI and ERDF for funding.

Notes and references


