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FEATURE ARTICLE

Metallodendrimers: metal ions as supramolecular glue†

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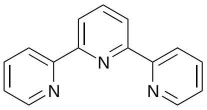
The coordination of appropriate organic molecules containing multiple metal-binding domains to metal ions provides a versatile alternative to carbon–carbon or carbon–heteroatom bond formation for the assembly of dendrimers.

Introduction: metallosupramolecular chemistry

In the past two decades, dendritic molecules have developed from laboratory curiosities to components of burgeoning new technologies.[1] The majority of dendrimers are purely 'organic', with the descriptor 'organic' referring both to the chemical character of the molecular components used in the assembly and to the type of chemical reaction used in their combination. Conventionally, dendrimers are prepared with key assembly steps which involve the formation of carbon–carbon or carbon–heteroatom bonds. Although this methodology is well developed, it has a number of inherent disadvantages; whilst such bonds tend to be kinetically stable once formed, there may be significant energy barriers to their formation.

We have developed metallosupramolecular chemistry, in which the characteristic and preferred coordination numbers and geometries of metal ions are matched with the inherent bonding characteristics of polydentate ligands to control the assembly of novel supramolecular architectures.[2] A basic concept is that of a ligand domain as a metal-binding motif which may be introduced into multifunctional ligands. In our studies, we have adopted oligopyridine metal-binding domains as our favoured motif and, for reasons documented elsewhere, we have concentrated upon 2,2′:6′,2″-terpyridine **1** (tpy) domains.[3]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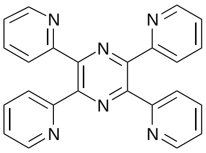
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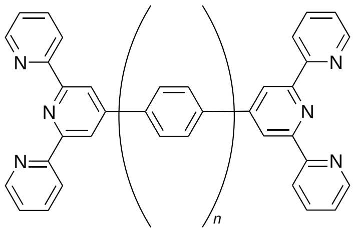
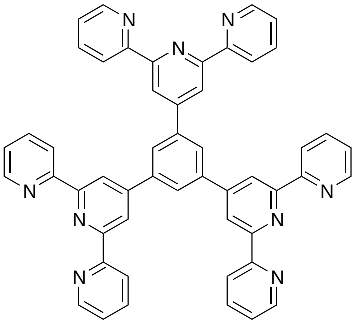
We and others[4,5] have developed metallosupramolecular approaches to dendrimers in which the key growth steps involve metal-donor atom interactions as opposed to carbon–carbon or carbon–heteroatom bond formation. This methodology is predicated on the thermodynamic and kinetic features of coordinate bond formation as opposed to conventional covalent bond formation. We describe such systems as metallodendrimers, and they may bear multiple functionality at inner generations or at the surface generation. Dendritic systems incorporating metal centres are of current interest as novel magnetic, electronic or photo-optical materials.

Building metallodendrimers: prototype systems

The simplest methodology relies upon the synthesis of organic molecules bearing two or more metal-binding domains, which are subsequently combined with the complementary metal components to give the desired metallodendrimers. When the tpy-based ligands are used, a six-coordinate metal centre is the appropriate complement to two tpy domains. In general, this approach leads to divergent or near-divergent syntheses. Our initial studies involved the prior synthesis of ligands containing two or more tpy metal-binding domains. Although we did not initially consider the simplest condensed bis(tpy) system, 2,3,4,5-tetra(2-pyridyl)pyrazine **2** (tppz), this, together with related pyrazine derivatives, has proved to be a useful bridging ligand[6] and we have recently embarked upon its incorporation into metallosupramolecules.[7] The first generation of ligands consisted of covalently linked tpy domains with variable length spacers **3** and the study of these compounds led to a continuing collaboration with the group of Jean-Pierre Sauvage in Strasbourg. We utilised the 'complexes as metals, complexes as ligands'[4] approach and the new ligands behaved very much as expected and gave us valuable experience in the assembly of low-nuclearity metallodendrimers.[8–11] This approach allowed the synthesis of multinuclear systems designed to give directional and spatial control over electron and/or energy transfer in components of photoconversion systems. Simple developments of the ligand syntheses lead to **4**, the progenitor of a metallosupramolecular starburst system.[11]


3 n = 0–4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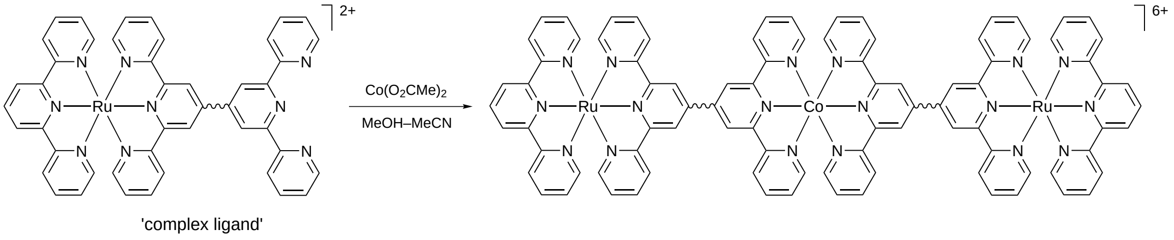
However, there were a number of inherent disadvantages with the methodology we had developed. Firstly, we were spending ever more time in ligand design and synthesis, and secondly, the routes tended to be divergent. In addressing the latter problem, we became concerned with the genesis of a convergent approach utilising labile first-row transition-metal centres in combination with kinetically inert ruthenium(II) centres (Scheme 1).[10] In the example shown, the reaction is essentially quantitative and is complete in minutes, in contrast to the formation of the corresponding triruthenium complex in lower yield after several hours at reflux. Subsequent oxidation gives a kinetically inert cobalt(III)diruthenium(II) complex. This approach partially overcame the problems associated with the

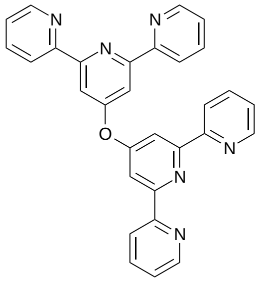


Scheme 1

divergent synthesis, but we were aware that many of the advantages of the metallodendritic approach would be lost if time-consuming ligand synthesis was an essential prerequisite.

Metal-directed reactions: *in situ* ligand synthesis

In the next phase of our work, we decided to develop *in situ* ligand assembly reactions to avoid the prior synthesis of bridging ligands. We had previously shown that the electrophilic character of 4-halopyridines was dramatically enhanced upon coordination to a transition metal[8,12] and we now extended this methodology to the *in situ* synthesis of the ether-bridged ligand **5**. The key components are the nucleophilic organic compound **6** and the electrophilic 4′-chloro-2,2′:6′,2″-terpyridine (Cltpy) complex **7** and reaction proceeds smoothly in the presence of base to give **8** in excellent yield (Scheme 2). The formation of **5** was established unambiguously by an X-ray structural determination of ligand prepared in a metal-free synthesis.[13]



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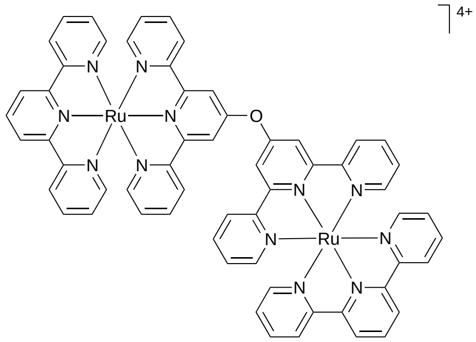
We had hoped to extend the methodology to the direct formation of multinuclear complexes by the reactions of complexes of **6** with **7**; however, coordination of **6** to a metal sufficiently reduces its nucleophilicity that it does not react with **7**. However, **8** contains a non-coordinated tpy domain and so may be further reacted with appropriate metal species. Typical reactions have involved termination to yield dinuclear species **9** or the convergent assembly of trinuclear species with central iron, cobalt or ruthenium centres using the route shown in Scheme 1. It also proved to be possible to prepare **10** from the reaction of $[\mathrm{Ru(Cltpy)_2}]^{2+}$ with **6**; this is a complex which can act as a bridging ligand.



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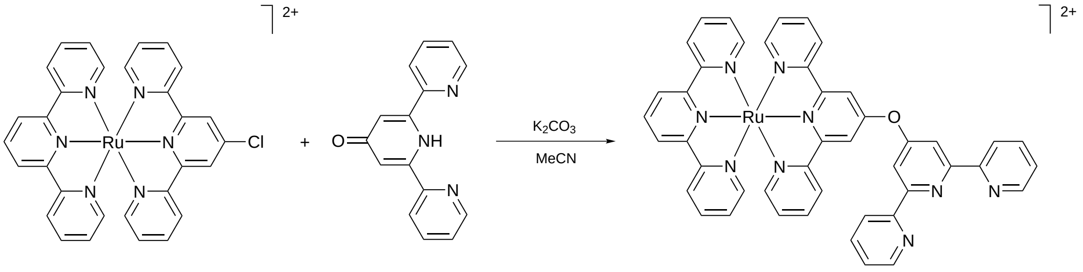
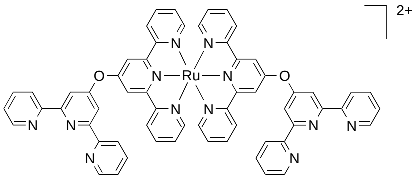
The next question related to the formation of higher generations using this methodology. The key compound **11** could be prepared in good yield from the divergent reaction of **10** with $[\mathrm{Ru(Cltpy)Cl_3}]$ or the convergent reaction of $[\mathrm{(Cltpy)Ru(}$**5**$\mathrm{)}]^{2+}$ with ruthenium trichloride. Analogues could be prepared using extensions of Scheme 1 with $[\mathrm{(Cltyp)Ru(}$**5**$\mathrm{)}]^{2+}$. We had hoped to react the surface Cltpy ligands with



7 **6** **8**

Scheme 2



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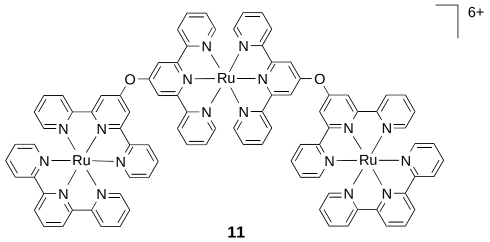

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additional **6** to create new surface tpy metal-binding sites. However, it turned out that further homologation is not possible and that attack of **6** at a surface generation Cltpy is disfavoured compared to attack at inner generation ether links to give mononuclear complexes of **5** and **6** as the major products.

At this stage, we had shown that metal-directed reactions of a coordinated electrophile could be used for the formation of ether linkages within a given generation, but those new bonds were not stable under the reaction conditions required for the use of analogous reactions at later generations. Furthermore, the only control over topology and morphology came from the design of the ligand containing the multiple tpy domains.

A second *in situ* synthesis

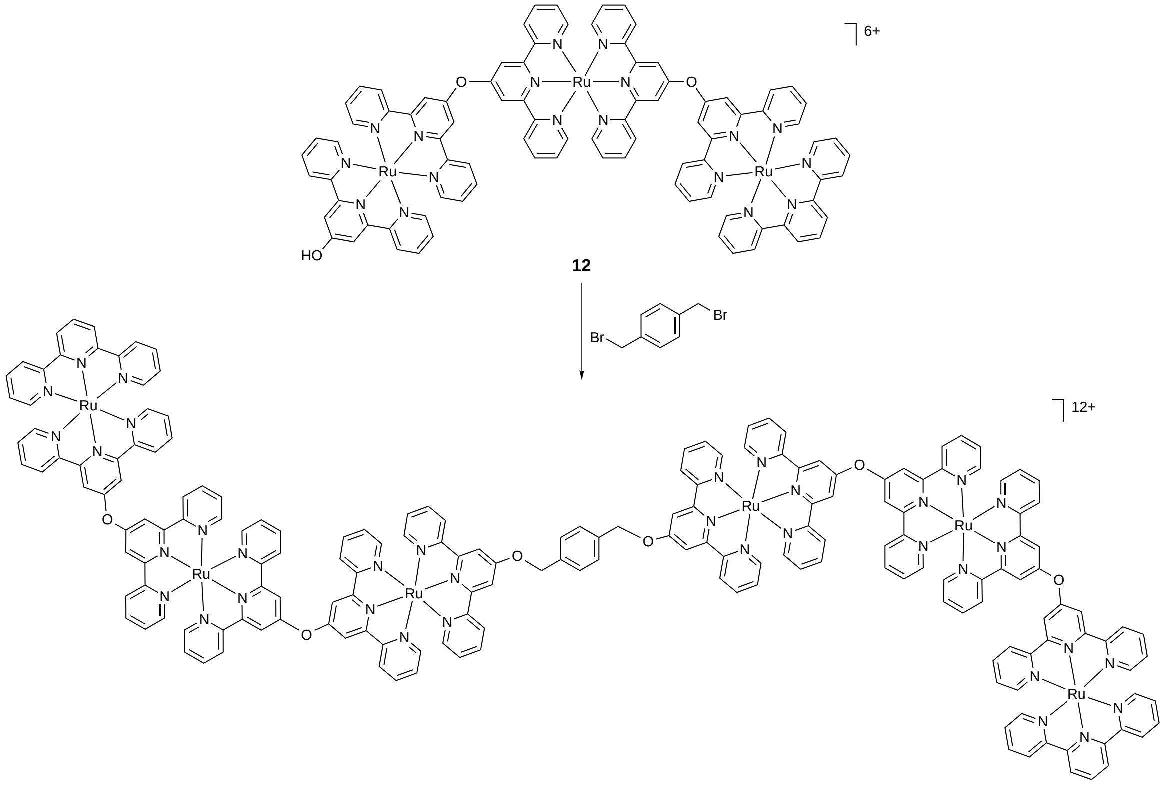
We noted above that complexes of **6** would not react with coordinated Cltpy electrophiles. We wondered if the use of a better electrophile might be successful and investigated the reactions of coordinated **6** with benzyl halides. In particular, we felt that the use of bis(bromomethyl)benzenes would lead to linear growth reactions. Furthermore, it was not necessary to use mononuclear complexes containing **6**, the ready accessibility of multinuclear complexes using the routes described above meant that it would be possible to incorporate building containing variable numbers and types of metal centres. This approach proved successful and a typical reaction leading to a hexanuclear species is shown in Scheme 3.[14] It is also interesting to note that this change in methodology also leads to a convergent synthesis; the hexanuclear species is formed from two trinuclear intermediates. The reaction with the electrophile occurred without any consequence for inner generation ether linkages and we could use the reaction of a coordinated electrophile with a nucleophile for the formation of one generation and the reaction of a coordinated nucleophile with an electrophile to prepare the subsequent generation.

We also noted that the convergent approach would permit us to bring more than two subunits together, and this led us to investigate the use of a 1,3,5-tris(bromomethyl)benzene centre for the assembly of three subunits. This approach was also successful and allowed the synthesis of a range of high-nuclearity species including a nonanuclear complex.[14] Finally, we considered the reaction with hexakis(bromomethyl)benzene—when the trinuclear complex **12** was used, a convergent synthesis of an octadecanuclear complex should result. Although we worried that steric interactions might prevent the reaction from proceeding to completion, we were very pleasantly surprised to find that **12** reacted smoothly with hexakis(bromomethyl)benzene to give the desired octadecanuclear species **13**.[15]

A return to classical strategies

At this point, the use of the benzene central growth point led us to reconsider some aspects of our strategy. Although we had adopted the metallodendritic approach to circumvent kinetic barriers experienced in ‘pure’ organic chemistry, it now seemed that we could use high-yielding ‘organic’ reactions for the preparation of the central site of the dendrimer, with subsequent generations being built using the metallodendritic methodology. Preliminary experiments in collaboration with George Newkome established the viability of this hybrid approach, although we found the complexity of the organic components involved to be discouraging.[16]

We decided to adopt pentaerythrytol as a cheap and readily available starting point. The reaction of pentaerythrytol with an excess of Cltpy gave **14** with four tpy domains in excellent yield;[17] in contrast, when the pentaerythrytol was in excess, the monofunctionalised compound **15** could be isolated.[18] A related ligand **16** incorporating six tpy domains is readily prepared from dipentaerythrytol. The growth of metallodendrimers from **14** and **16** is facile; reaction with [Ru(Xtpy)Cl_3] gives the expected first generation tetranuclear or hexanuclear complexes in excellent yields. One of current interests lies in the incorporation of pendant functionality at the surface generation in high-nuclearity metallodendrimers and the a 40-boron first-generation *ortho*-carbaboranyl-functionalised metallodendrimer **17** is a typical example of such compounds.[17]



Scheme 3

The new building block **15** now allows us to use a genuinely dendritic approach for the synthesis of metallodendrimers. The key species is **18**, which is a surface generation Xtpy functionalised species. However, in this case, the X-functionality incorporates three nucleophilic hydroxy groups. Subsequent reaction with the electrophilic complex **7** yields the expected hexadecanuclear complex.[18]

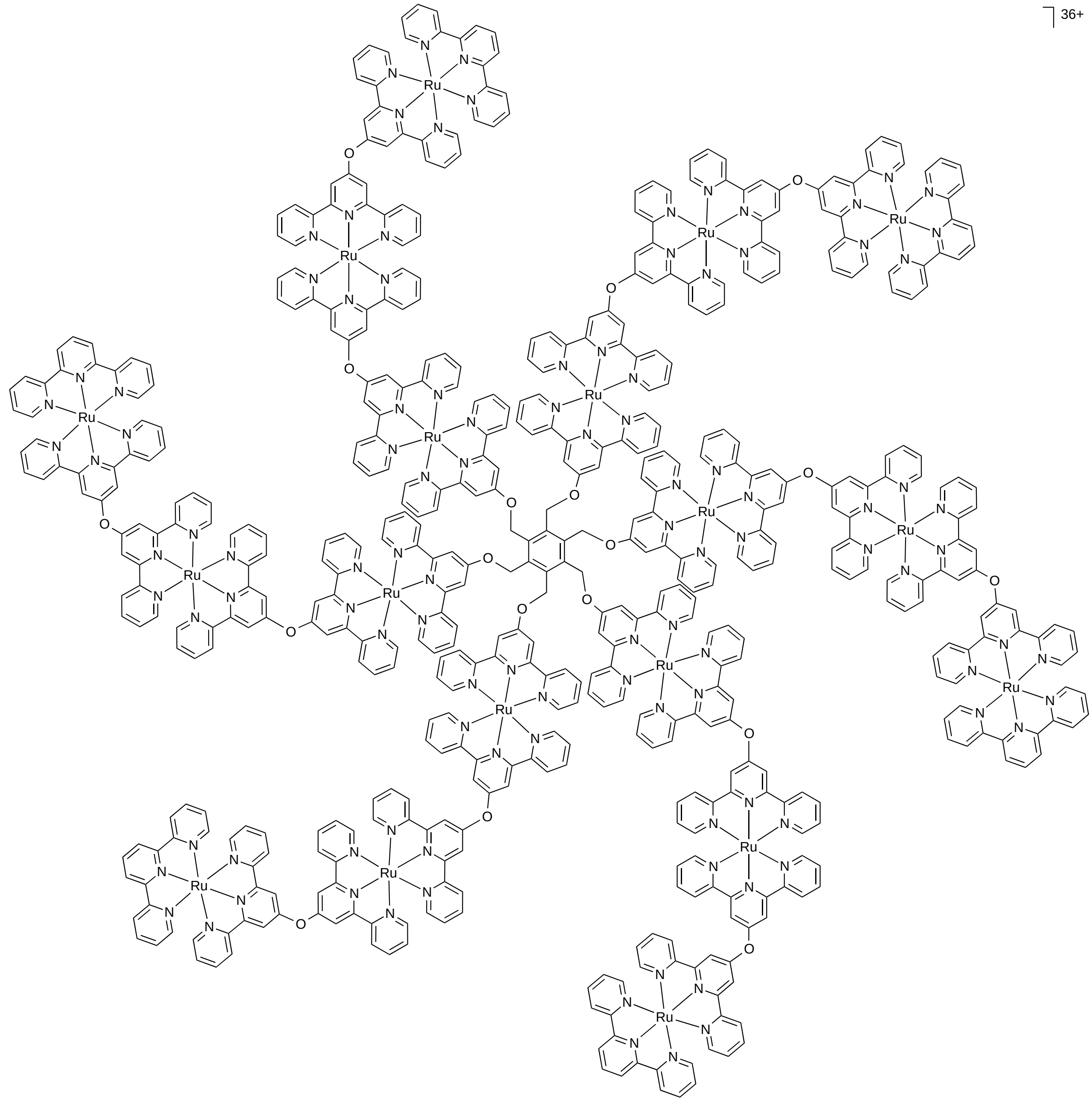
Metallocentric dendrimers

The strategies discussed above proved effective, but there were still a number of problems associated with the use of carbon-based central units. Firstly, the connectivity will be related to the three common geometries observed at carbon: linear, trigonal planar or tetrahedral and increases in connectivity can only be associated with an increase in the complexity of the central unit. Secondly, a central tetrahedral carbon centre with four identical (non-chiral) groups attached cannot function as a site for chiral initiation. In chiral dendrimers, the chirality cannot commence at a central carbon bearing four identical groups. These considerations led us to our final development to using a metal centre for dendrimer initiation.

Our rationale was quite simple and based upon a number of established features from coordination chemistry. The connectivity (coordination number) at a metal may vary from two to twelve with a wide range of coordination geometries possible. For example, four-coordinate metal centres may be square-planar or tetrahedral, in contrast, four-coordinate carbon is almost invariably tetrahedral. In addition, six-coordinate metal bonded to three didentate chelating metal-binding domains are inherently chiral, with Δ and Λ enantiomers. This point must be stressed, a metal centre bearing three identical didentate chelating ligands is inherently chiral.

Divergent metallocentric metallodendrimers

We initially considered a divergent approach to metallocentric systems based upon a central {M(bpy)$_3$} (bpy = 2,2′-bipyridine) unit based upon our earlier metal-directed



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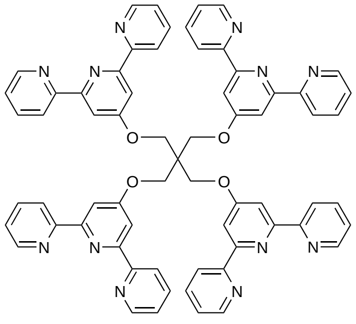
methodology. To establish the principle, we prepared $[Ru(Cl_2bpy)]^{2+}$ (Cl_2bpy = 4,4′-dichloro-2,2′-bipyridine) which can, in principle, be resolved into Δ and Λ enantiomers. The coordinated halopyridine is activated towards attack by nucleophiles and the complex reacts smoothly with **6** to give a complex bearing six non-coordinated tpy domains distributed about a central, chiral, metal site. We planned the incorporation of the next generation by reaction of this species with $[Ru(tpy)Cl_3]$ (Scheme 4). This combination of chiral $\{M(bpy)_3\}$ and achiral $\{M(tpy)_2\}$ domains should avoid problems of diastereoselectivity associated with metallodendrimers based upon $\{M(bpy)_3\}$ domains alone. Unfortunately, this resulted in an inseparable mixture of compounds in which five or six sites had reacted. Clearly, steric constraints are becoming paramount in this divergent approach and we are currently designing suitable spacer groups for incorporation between the bpy and tpy domains. However, in addition to this longer term strategy, we also wondered if the steric problems might be relieved by the adoption of an alternative convergent metallocentric strategy.



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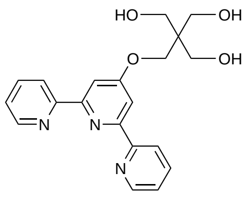

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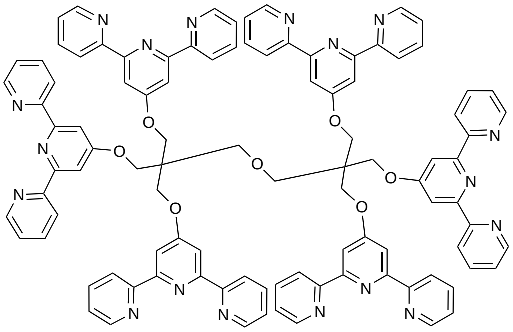

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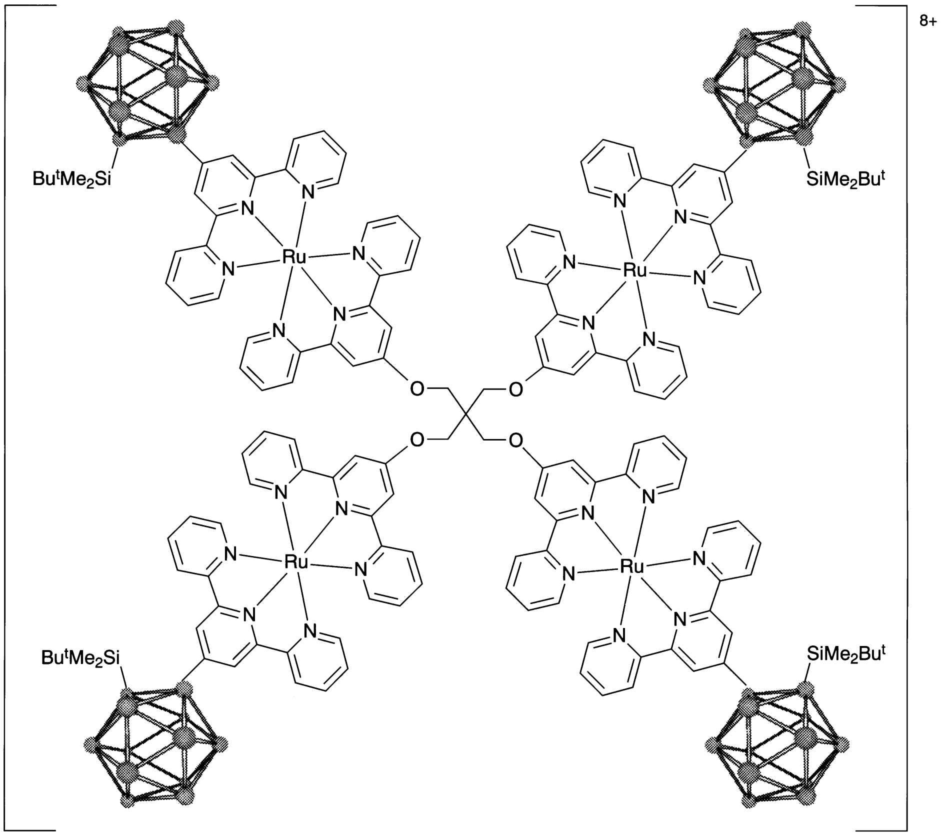
Convergent metallocentric metallodendrimers

In our latest development, we combine many of the strategies discussed earlier. We commence by reacting a coordinated **6** ligand with an excess of a good electrophile to give a new complex **19** with an electrophilic site remote from the metal which can subsequently be reacted with a nucleophile (Scheme 5). We have selected 4,4′-dihydroxy-2,2′-bipyridine as a nucleophile which contains a didentate metal-binding domain that will eventually be used to generate a potentially chiral $\{M(bpy)_3\}$ domain. The product **20** is a dinuclear complex in which two $\{Ru(tpy)_2\}$ domains are linked by a non-coordinated bpy domain; in essence, this complex is simply a disubstituted 2,2′-bipyridine, which is expected to coordinate rapidly to labile first-row transition-metal ions such as iron(II) or cobalt(II). The reaction of the dinuclear complex **20** with either iron(II) or cobalt(II) is indeed rapid and leads to the convergent assembly of the desired heptanuclear metallocentric metallodendrimer **21** in near quantitative yield.

These convergent and divergent metallocentric methodologies are in many senses complementary. The divergent methodology allows the stereoretentive incorporation of predefined chirality (Δ or Λ) at the central metal site, whilst the convergent synthesis leads to a racemic mixture of the two enantiomers in the absence of chiral auxiliaries. We are presently designed a series of surface generation chiral tpy



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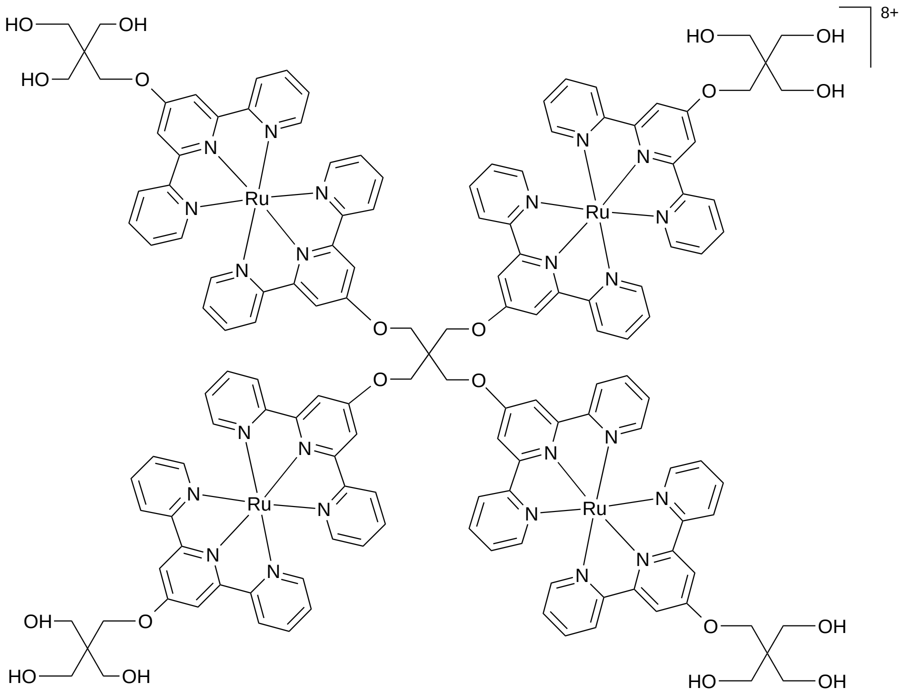

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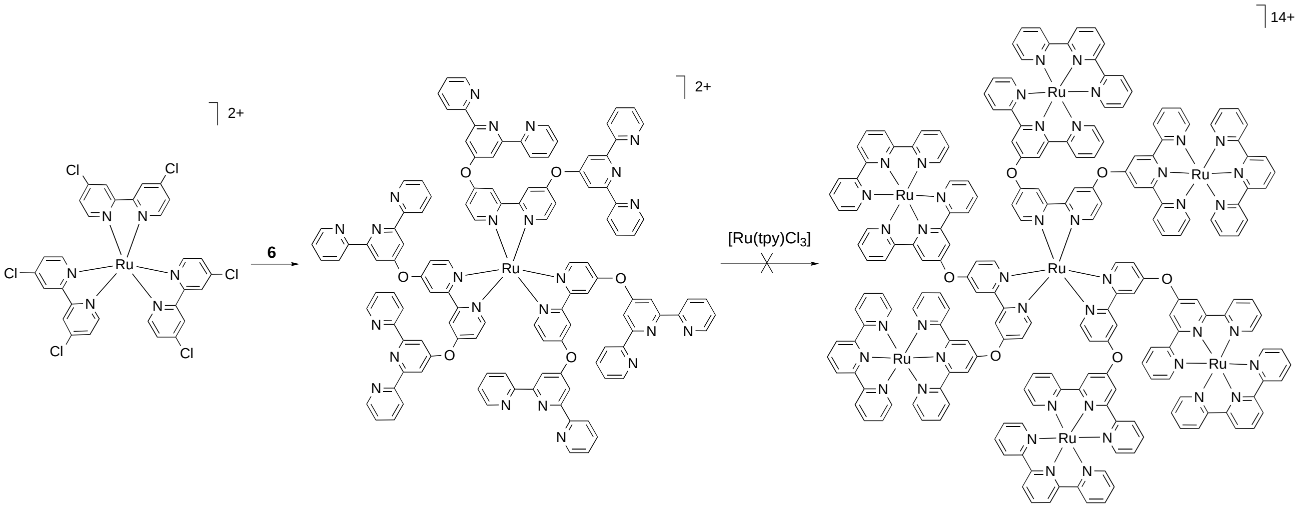
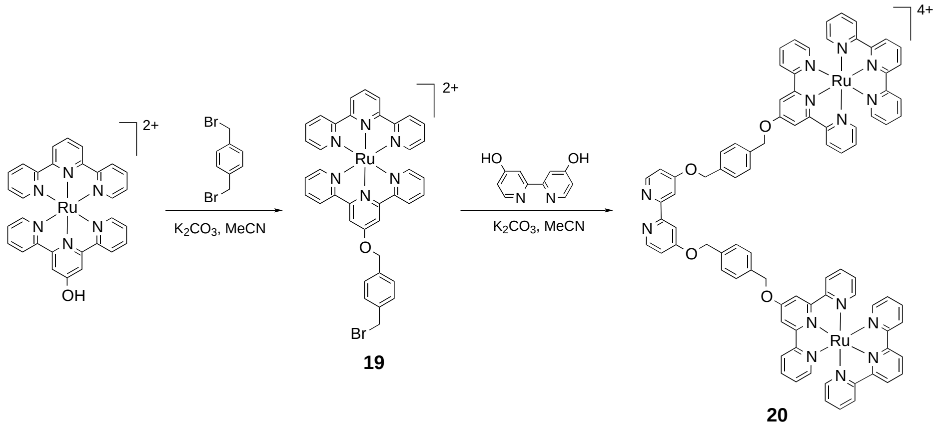
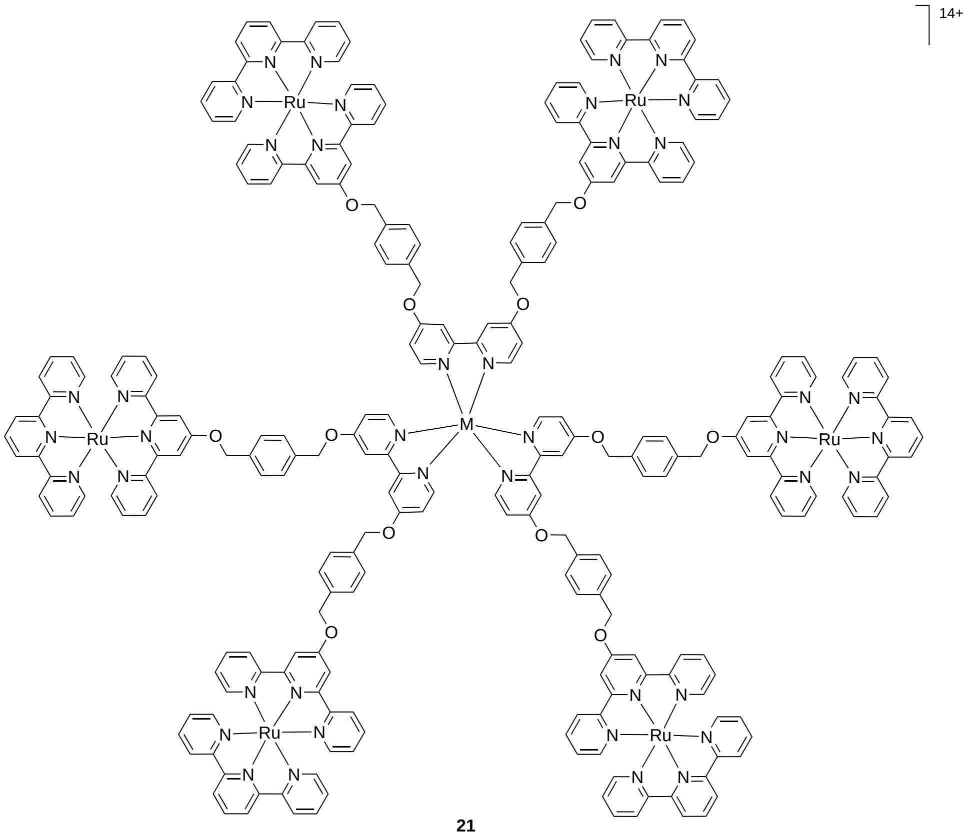


Scheme 4



Scheme 5



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ligands to impose diastereoselectivity in the convergent synthesis. However, the two strategies are also fundamentally different. In the divergent case, the chiral information is propagated outwards as the dendrimer grows. In contrast, the use of chiral auxiliaries in the surface generation may allow the resolution to occur at the final stage through information transfer in an ‘inwards’ sense.

Some concluding remarks

I hope that this brief overview of metallodendritic chemistry serves to emphasise some of the advantages of the methodology. The structures are attractive and the molecules themselves are tractable and may be fully characterised by the conventional techniques of the molecular chemist. Solubility is controlled by the counterions; the chloride salts are water and methanol soluble, the hexafluorophosphate salts dissolve in acetonitrile or acetone, and the tetraphenylborate salts may be dissolved in dichloromethane.

Acknowledgements

It remains to thank the talented and hard-working coworkers who have been and are involved in this work: the initial studies of metallodendrimers were made by Dr Alex Cargill Thompson in his doctoral and post-doctoral studies and continued by Peter Harverson, who has developed the complementary electrophile–nucleophile sequences in his doctoral studies. The pentaerythrytol systems are part of the doctoral work of Dave Phillips and Marco Cattalini, with the cluster-functionalised surface generations being studied by Marco and Dr Dominique Armspach. The metallocentric systems have been studied by Pete Harverson and Dr Martin Oberholzer. The cluster-functionalisation is part of a wider collaborative project with Dr Catherine Housecroft. I should also like to thank the EPSRC, the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung, the University of Basel and Ciba-Geigy plc for support. This work is part of a continuing collaborative effort involving groups in Basel, Bologna and Strasbourg.

Footnotes

† This ChemComm is also available in enhanced multi-media format *via* the World Wide Web: http://chemistry.rsc.org/rsc/cccenha.htm

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Edwin Constable was born in Edinburgh, Scotland. In 1978 he obtained a first class honours degree in chemistry from St Catherine’s College, Oxford; he remained in Oxford to undertake research in the design of photocatalysts under the supervision of Dr K. R. Seddon. In 1980 he received a DPhil and a SERC post-doctoral fellowship enabled him to conduct research in macrocyclic chemistry with Professor J. Lewis, University of Cambridge. After a research fellowship from the Commissioners for the Exhibition of 1851 he held a demonstratorship and lectureship at the University of Cambridge. In 1993 he moved to a chair of Inorganic Chemistry at the Institute for Inorganic Chemistry, University of Basel. He has held visiting professorships at the Université Louis Pasteur, Strasbourg, the University of Capetown and the University of Pavia. His research interests cover many aspects of supramolecular and coordination chemistry.

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