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COORDINATION CHEMISTRY REVIEWS

The synthesis of 2,2′:6′,2″-terpyridine ligands — versatile building blocks for supramolecular chemistry

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Abstract

The tridentate ligand 2,2′:6′,2″-terpyridine is becoming increasingly widely used. Appended substituent groups may be utilized to tailor the properties of its complexes. 2,2′:6′,2″-

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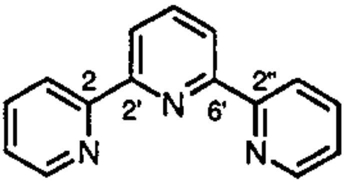
Terpyridine ligands incorporating other metal binding functionalities and multinucleating ligands incorporating two or more terpyridine moieties may be used to assemble supramolecular coordination oligomers. The synthetic strategies used to prepare 2,2′:6′,2″-terpyridine ligands are reviewed comprehensively.

Keywords: Tridentate ligands; Synthesis; Supramolecular coordination oligomers

1. Introduction

Since the tridentate ligand 2,2′:6′,2″-terpyridine (tpy, 1) was first prepared over 60 years ago [1,2], its coordination chemistry, along with that of its substituted (Xtpy) analogues, has been widely studied [3]. 4′-Aryl-substituted-2,2′:6′,2″-terpyridines have been found to be highly sensitive reagents for the colorimetric determination of iron(II) [4], with some finding potential applications in clinical chemistry [5–11]. More recently, 2,2′:6′,2″-terpyridines have found increasing favour as coordination chemistry has started to shift from the molecular to the supramolecular level. Substituent groups on the ligands may be used to tailor the properties of the resulting coordination complexes. Chiral 2,2′:6′,2″-terpyridine ligands are being designed as reagents for enantioselective synthesis [12–14]. Appropriately functionalized 2,2′:6′,2″-terpyridines have been anchored to oxide surfaces, permitting the build up of a monolayer or a thin film of coordination complexes [15,16]. Electron-withdrawing and -releasing substituents may be used to alter the redox and photophysical properties of the complexes [17–19]. Electron-withdrawing substituents may also be used to render $[Ru(Xtpy)_2]^{2+}$ complexes luminescent at room temperature [20]. Aryl substituents increase the extinction coefficients of metal-to-ligand charge transfer transitions of complexes [4,21]. A logical extension of such systems has been to attach pendant redox-active moieties, e.g. ferrocene [22–28], and metal binding functionalities, e.g. porphyrins [29–31], catechol [32,33] and macrocycles [34,35] to such ligands. The ability of 2,2′:6′,2″-terpyridine to chelate to a wide range of metal ions has lead to its incorporation in macrocyclic ligands [36–44], and lanthanide complexes of 2,2′:6′,2″-terpyridine ligands with multiple pendant carboxylate groups are attracting interest as luminescent agents for protein labelling [45–48].



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There has been considerable recent interest in metallosupramolecular species constructed from a number of metal ions linked by suitable ligands containing two or more sets of potential donor atoms. If such ligands are dinucleating, then linear oligomers and polymers may be formed. If, instead, the ligand contains three or more donor sets, then two- and three-dimensional metallosupramolecular arrays can be created. Much of the interest in these species is derived from the possibility of photoinduced electron- or energy-transfer from one metal centre to the next if a suitable energy gradient exists in the complex. Thus, suitably designed linear oligomers may act as molecular wires, while two- and three-dimensional species may be used for the harvesting of light energy [49,50].

The design of 'back-to-back' ligands incorporating two 2,2′:6′,2″-terpyridine moieties which may be used to bridge metal centres is therefore finding particular favour at the moment [4,26,29,31,51–57]. Mixed-metal ruthenium(II)–osmium(II) complexes linked by a variety of such ligands incorporating spacers designed to vary the degree of conjugation as well as the metal-to-metal separation have been found to exhibit efficient ruthenium to osmium energy transfer [50,56,58]. Indeed, the symmetry of 4′-substituted-2,2′:6′,2″-terpyridines, combined with the ability of many metal ions to coordinate two such tridentate ligands in a pseudo-octahedral manner giving a single achiral isomer, makes 2,2′:6′,2″-terpyridine units ideal metal binding domains for use in coordination oligomers and other metallosupramolecular systems [52,59,60].

The aim of this article is to review comprehensively the methods, strategic or otherwise, that have been used to prepare 2,2′:6′,2″-terpyridine, substituted-2,2′:6′,2″-terpyridines, and indeed any ligands incorporating 2,2′:6′,2″-terpyridine units. Annelated derivatives of 2,2′:6′,2″-terpyridine are also covered, though in somewhat less depth. My intention is to provide a source of reference for coordination chemists wishing to design 2,2′:6′,2″-terpyridine-based ligands to whatever end. For any omissions or errors, I offer my apologies. The coordination chemistry of the ligands is on the whole outside the scope of this review and the reader is therefore referred to the relevant papers and other publications by the appropriate authors.

The general synthetic strategies used to create 2,2′:6′,2″-terpyridine ligands are outlined in Section 2). The syntheses of 2,2′:6′,2″-terpyridine its *N*-oxides and substituted derivatives are reviewed comprehensively in Section 3), grouped according position of substitution. 2,2′:6′,2″-Terpyridine ligands incorporating other metal binding domains are discussed in Section 4), and multinucleating ligands incorporating two or more 2,2′:6′,2″-terpyridine functionalities are collected in Section 5). Annelated derivatives of 2,2′:6′,2″-terpyridine are introduced in Section 6), and the conformations and solid-state structures of 2,2′:6′,2″-terpyridine ligands are discussed briefly in Section 7).

2. Synthetic strategies

The two general strategies commonly used in the synthesis of 2,2′:6′,2″-terpyridines involve either the coupling of pyridine units, or the synthesis of either the central or, more rarely, the two terminal pyridine rings.

2.1. Coupling methodologies

Early attempts at the synthesis of the oligopyridines utilized coupling methodologies, but tended to lack finesse, with convoluted processes being required to separate the numerous products from the reaction mixture. Coupling reactions may either involve the oxidative dehydrogenation of a pyridine, or the reaction of a halopyridine with a metal or a low oxidation state metal complex.

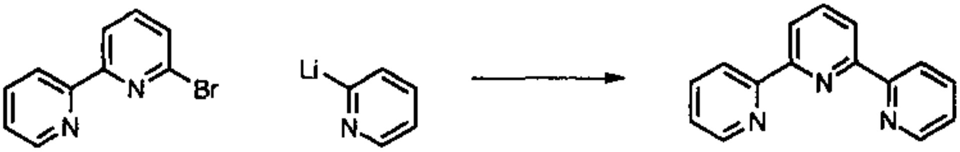
Morgan and Burstall first isolated 2,2′:6′,2″-terpyridine in the 1930s from a mixture of 20 or so compounds obtained from the oxidative coupling of pyridine by iron(III) chloride at elevated temperature and pressure in a steel autoclave [1,2]. Typically, 8 kg of pyridine afforded less than 100 g of 2,2′:6′,2″-terpyridine. Analogous dehydrogenation reactions using a variety of other metallic chlorides were also investigated, though these were found to be less successful than the iron(III) chloride coupling [61]. The mixed Ullman couplings either of 2-bromopyridine with 2,6-dibromopyridine or of 2-bromopyridine with 6-bromo-2,2′-bipyridine using metallic copper are both inefficient; significant amounts of the symmetrical coupling products 2,2′-bipyridine and 2,2′:6′,2″:6″,2‴-quaterpyridine are obtained in each case [62]. Equimolar quantities of pyridine and 2,2′-bipyridine may be coupled oxidatively using iodine to give 2,2′:6′,2″-terpyridine in 3% yield [62], while Raney nickel can be used to couple pyridine dehydrogenatively to give 2,2′-bipyridine along with traces of 2,2′:6′,2″-terpyridine [63]. All of these methods produce yields of under 10% of the desired 2,2′:6′,2″-terpyridine, which is only isolated from the crude reaction mixture after protracted separation and purification processes.

In recent years, more strategic approaches have been developed using increasingly sophisticated organometallic coupling methods. The first such approach involved the reaction of 2,2′-bipyridine with 2-pyridyllithium (obtained from the lithiation of 2-bromopyridine using *n*-butyllithium) in ether at −40 °C affording 2,2′:6′,2″-terpyridine in 39% yield (Scheme 1) [64]. A novel dihydroterpyridine has also been isolated as a by-product of this reaction [65]. Wakabayashi and co-workers have increased the yield to 65% by coupling 2-pyridyllithium with 6-ethylsulphinyl-2,2′-bipyridine, the sulphoxide obtained from the oxidation of 6-ethylthio-2,2′-bipyridine by magnesium monoperoxyphthalate (Scheme 2) [34].

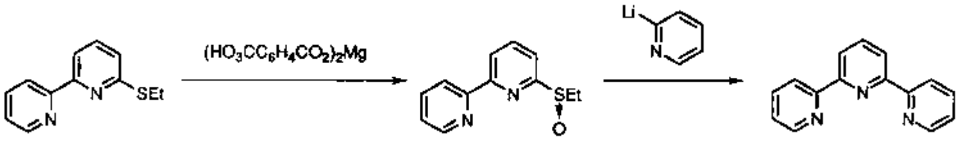
2.2. Ring assembly methodologies

2.2.1. Assembly of the central ring

Perhaps the most effective, and certainly the most widely used general strategy for the synthesis of 2,2′:6′,2″-terpyridines is to assemble the central pyridine ring of



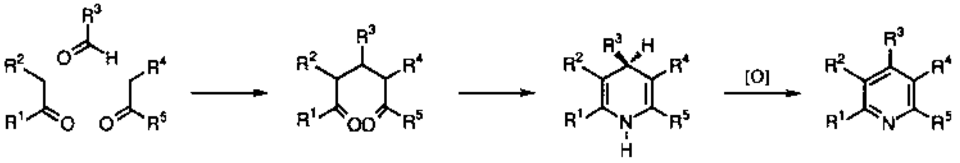
Scheme 1.



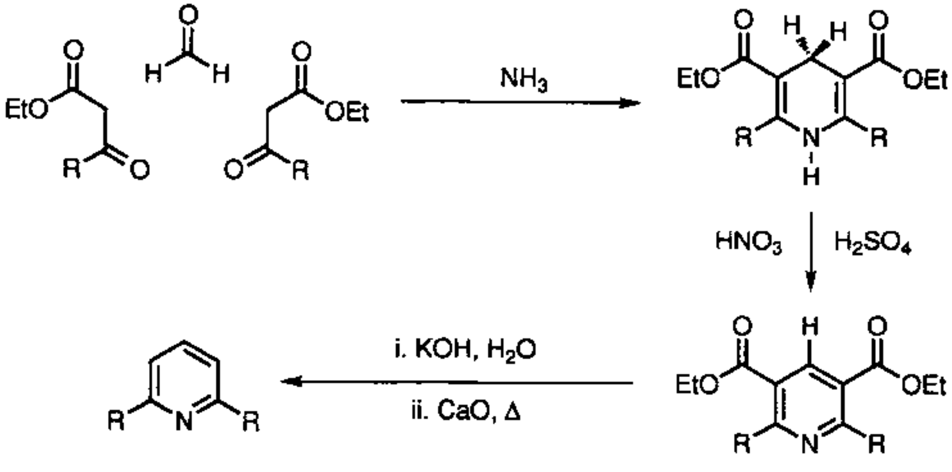
Scheme 2.

the ligand [4]. This is achieved (Scheme 3) by the condensation of two ketones with an aldehyde to give a 1,5-diketone, which may or may not actually be isolated. Ring closure is effected using ammonium acetate [4,66], hydroxylamine [67], formamide [4], or acetamide [4]. In some cases, oxidative dehydrogenation of a dihydropyridine obtained as an intermediate is necessary. In the synthesis of a 2,2′:6′,2″-terpyridine, R^1 and R^5 would be 2-pyridyl groups, while R^2, R^3, and R^4 could be substituents as desired.

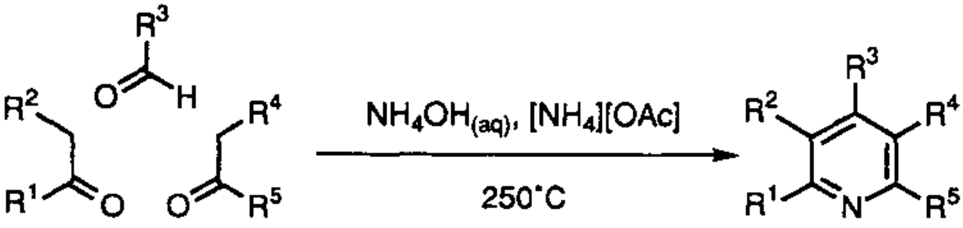
A wide variety of experimental and mechanistic techniques adopt this basic principle. The earliest methods developed used the pyridine syntheses devised by Hantzsch [68] and Tschitschibabin [69]. The Hantzsch pyridine synthesis (Scheme 4) involves the condensation of two equivalents of a 3-oxocarboxylate ester with an aldehyde, followed by cyclization with ammonia to give a dihydropyridine ester, which affords the pyridine upon oxidation with nitric acid. Saponification and



Scheme 3.

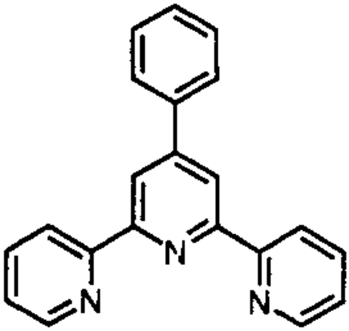


Scheme 4.



Scheme 5.

then decarboxylation of this ester gives the desired 2,6-disubstituted pyridine [68]. The Tschitschibabin pyridine synthesis (Scheme 5) involves the one-pot co-condensation of two ketones and an aldehyde in aqueous ammonia, with catalytic amounts of ammonium acetate, at elevated temperatures and pressures [69]. Frank and Riener have used this method to synthesize 4′-phenyl-2,2′:6′,2″-terpyridine (**2**) in



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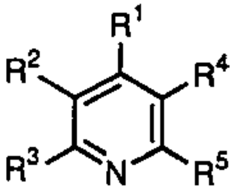
17% yield from 2-acetylpyridine and benzaldehyde [67]. The drawbacks of the Tschitschibabin synthesis are the rigorous reaction conditions required, the low yields eventually obtained from the extraction of the crude reaction mixture, and the tendency in some cases to form alternative products [70] such as **3**. Weiss improved the Tschitschibabin reaction by altering the conditions to those utilizing ammonium acetate in glacial acetic acid at reflux [66].

The desire to improve yields and product specificity led to the development of various multistep synthetic strategies. The basis of these (Scheme 6) is the aldol condensation of 2-acetylpyridine (or a substituted derivative) with an aldehyde in basic aqueous or alcoholic media to give an α,β-unsaturated ketone or enone, **4**. Michael addition of a suitable enolate then affords a 1,5-diketone, **5**. The potassium enolate of 2-acetylpyridine can, for instance, be prepared in situ by the action of potassium *t*-butoxide [71]. Ring closure with ammonium acetate results in the formation of a dihydropyridine, which undergoes aerial oxidation to the desired terpyridine. In practice, however, the conditions required to make the enone are not



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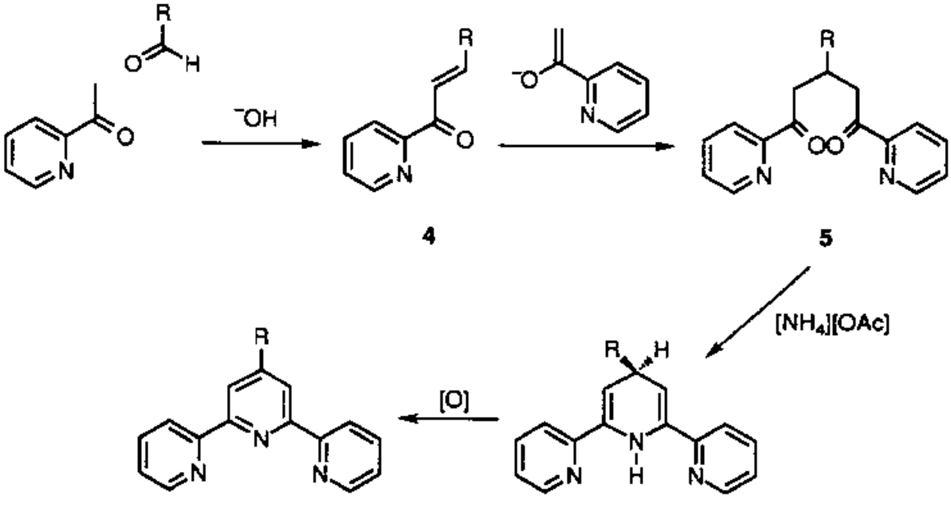
compatible with those needed for the enolate. Furthermore, such enones tend not to be isolable unless the substituent R is aromatic, thus stabilizing the enone by conjugation [72].

In some instances, aromatic aldehydes react directly with two equivalents of 2-acetylpyridine to give a 1,5-diketone, **5**. This can be advantageous, provided a symmetrical 2,2′:6′,2″-terpyridine is the target, since the alternative 1:1 reaction yields an enone which must, in turn, be reacted with an enolate species to give the diketone in situ [36]. Use of a stoichiometric amount of 2-acetylpyridine is likely to favour the formation of the enone, while an excess favours the diketone. Low temperatures (0–10 °C rather than 20 °C) and short reaction times also favour isolation of the enone [73]. In some cases, direct formation of the diketone may be electronically or sterically hindered. It is, however, the author's experience that it is not always possible to predict which of the enone and the 1,5-diketone may be prepared from a given arylaldehyde. In some instances cyclohexanediols and cyclohexanols resulting



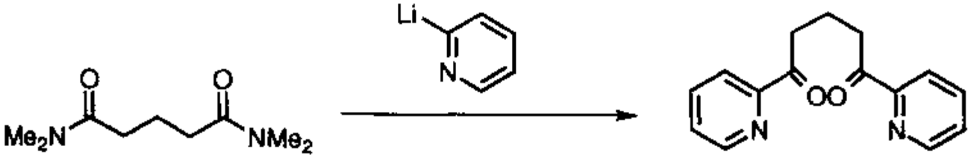
Scheme 6.

from the 3:1 and 3:2 condensation respectively, of 2-acetylpyridine and the arylaldehyde may instead be obtained [74]. Infrared spectroscopy allows diketones ($\nu_{C=O}$ typically 1698–1700 cm^{-1} [75–77]) to be distinguished from enones ($\nu C=O \sim 1670$ cm^{-1} [33,36,45,74]). The enones exhibit well-resolved ^1H NMR spectra with four aromatic resonances assigned to the pyridine ring and two at similar field assigned to the two *trans*-alkenyl protons. In contrast, the diketones often exhibit poorly resolved spectra, an observation which can be explained in terms of tautomeric processes occurring in solution [51]. Mass spectrometry can also be used to distinguish between enones and diketones, although thermal retro-reactions of the latter may yield enones.

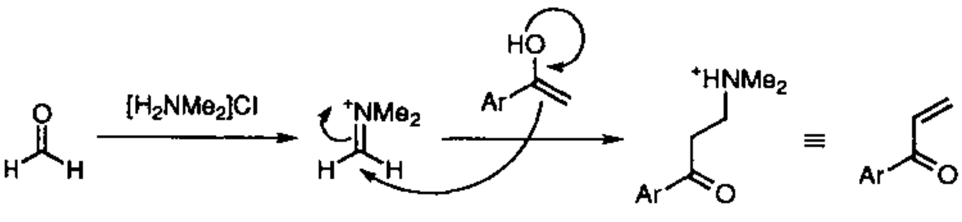
A direct route to symmetrical 1,5-diketones is that of Owsley et al. (Scheme 7), in which two equivalents of 2-pyridyllithium are reacted with *N*,*N*,*N*′,*N*′-tetramethylglutaramide [75]. Ring closure then gives the 2,2′:6′,2″-terpyridine in good yield [37].

Mannich bases offer viable synthetic alternatives to enones (Scheme 8) [78]. Paraformaldehyde and dimethylammonium chloride react to give an iminium ion, which has sufficient electrophilic character to attack enolizable ketones to give a Mannich salt.

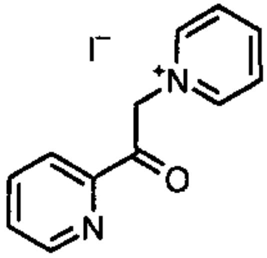
Acylpyridinium salts are versatile synthetic equivalents to enolates, although they are at a different oxidation level [4,79]. The acylpyridinium salt *N*-{1-(2′-pyridyl)-1-oxo-2-ethyl}pyridinium iodide (**6**) is obtained by the reaction of 2-acetylpyridine with iodine in anhydrous pyridine. The *N*-methylene hydrogen atoms are considerably more reactive than the methyl hydrogen atoms of the parent methyl ketone. A further advantage provided by the use of *N*-acylpyridinium salts is that the pyridinium group acts as an internal oxidant, effecting the dehydrogenation step required to aromatize the dihydropyridine obtained from the ring closure reaction. Kröhnke pioneered the use of *N*-acylpyridinium salts in this way in the stepwise synthesis of terpyridines [4].



Scheme 7.



Scheme 8.



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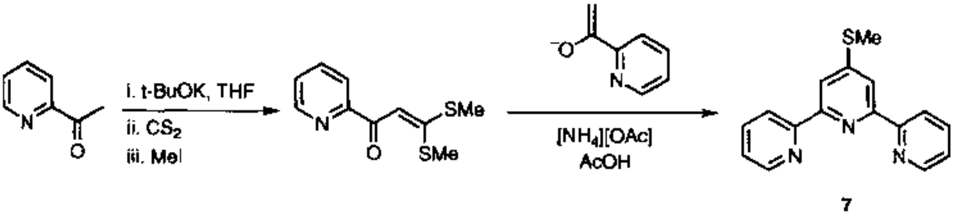
Constable's group have encountered difficulties in synthesizing the dimethylammonium chloride or pyrrolidinium chloride Mannich bases of 2-acetylpyridine in the conventional way [80]. A viable alternative is 2-(3-pyrrolidino-1-oxopropyl)pyridinium oxalate which can be produced by treating methyl-4-(1-pyrrolidino)butyrate with 2-lithiopyridine, followed by treatment with oxalic acid [81].

Potts and co-workers reported a high yield synthesis (Scheme 9) of the substitutionally versatile ligand 4′-methylthio-2,2′:6′,2″-terpyridine (**7**). The reaction of the potassium enolate of 2-acetylpyridine with carbon disulphide followed by methyl iodide gives an α-oxoketene dithioacetal, 3,3′-bis(methylthio)-1-(2-pyridyl)propen-1-one. Reaction with a further equivalent of the potassium enolate of 2-acetylpyridine affords an enedione intermediate, which gives **7** after in situ ring closure with ammonium acetate in glacial acetic acid at reflux [76,82–84].

Jameson and Guise recently reported an efficient two-step synthesis of 2,2′:6′,2″-terpyridine (Scheme 10) which can be carried out on a multigram scale [71]. An enaminone, prepared in high yield by the reaction of *N*,*N*-dimethylformamide dimethyl acetal with 2-acetylpyridine, is used as the enone in this reaction. This enaminone is condensed with the potassium enolate of 2-acetylpyridine, with loss of dimethylamine, and the resulting 1,5-dione is not isolated prior to ring closure by ammonium acetate.

Substituted analogues of 2-acetylpyridine can often be used instead of the parent compound in these methodologies, allowing substituents to be placed on either or



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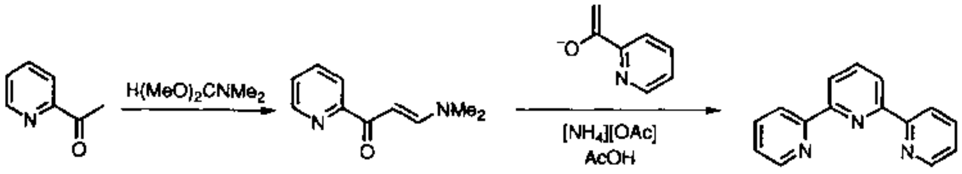
Scheme 9.



Scheme 10.

both of the two terminal rings of the terpyridine [21,36,37,72,85–87]. Clearly the two 2-acetylpyridine units must be added in a stepwise manner, via an enone or other intermediate, if an asymmetrically substituted product is desired [37], and for this reason, as well as its efficiency, Jameson's method is proving popular [12,44,88].

2.2.2. Assembly of the two terminal rings

The Kröhnke [89] and Potts [76,90] methods discussed above have been applied to the assembly of the two terminal pyridine rings of the 2,2′:6′,2″-terpyridine in a variety of 6,6″-diaryl-2,2′:6′,2″-terpyridines. Indeed, these reactions form the bases of syntheses of 2,2′:6′,2″:6″,2‴:6‴,2⁗-quinquepyridines [4,76].

Other ring assembly methods finding less general application are discussed below for the particular 2,2′:6′,2″-terpyridines in question.

3. Syntheses of specific 2,2′:6′,2″-terpyridine ligands

3.1. 2,2′:6′,2″-Terpyridine

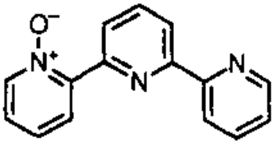
The Hantzsch methodology (Scheme 4) [68] can be used to prepare 2,2′:6′,2″-terpyridine in 30% yield from ethyl picolinoylacetate and formaldehyde [72]. The reaction of 2-(3-pyrrolidino-1-oxopropyl)pyridinium oxalate with *N*-{1-(2′-pyridyl)-1-oxo-2-ethyl}pyridinium iodide (**6**) and ammonium acetate, followed by coordination to iron(II) chloride affords the unsubstituted parent ligand 2,2′:6′,2″-terpyridine as its iron(II) complex. The free 2,2′:6′,2″-terpyridine is then obtained in 64% overall yield by oxidative cleavage of the complex with hydrogen peroxide [80].

Potts and co-workers have synthesized 2,2′:6′,2″-terpyridine by the reductive removal of the methylthio substituent from 4′-methylthio-2,2′:6′,2″-terpyridine (**7**) using Raney nickel [76] or nickel boride (generated in situ from sodium borohydride and nickel(II) chloride hexahydrate) [82]. In practice, the use of Raney nickel as reductant results in the contamination of the product with upwards of 15% 4′-ethoxy-2,2′:6′,2″-terpyridine [82], while the use of sodium borohydride makes this a costly route to 2,2′:6′,2″-terpyridine if performed on a multigram scale. Probably the most efficient synthesis of 2,2′:6′,2″-terpyridine is Jameson's two-step procedure discussed above which may be carried out on a multigram scale [71].

3.2. Syntheses of substituted 2,2′:6′,2″-terpyridines

3.2.1. 2,2′:6′,2″-Terpyridine-N-oxides

2,2′:6′,2″-Terpyridine-1-*N*-oxide (**8**) can be prepared by the oxidation of terpyridine by a stoichiometric amount of *m*-chloroperbenzoic acid, whilst an excess affords the 1,1″-di-*N*-oxide (**9**) [91]. In neither case is the 1,1′,1″-tri-*N*-oxide obtained, though the 1-*N*-oxide and the 1,1″-di-*N*-oxide can both be oxidized to it by hydrogen peroxide [91]. The action of hydrogen peroxide on 2,2′:6′,2″-terpyridine in glacial acetic acid solution is reported to yield 2,2′:6′,2″-terpyridine-1,1′,1″-tri-*N*-oxide (**10**) [92]. 2,2′:6′,2″-Terpyridine-*N*-oxides can be reduced back to the terpyridine ligand using phosphorus trichloride at reflux [92]. Comparison of the ^{1}H NMR spectra of the three *N*-oxides with that of the parent 2,2′:6′,2″-terpyridine indicates that the time-average transoid conformation is maintained [91].



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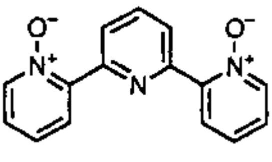

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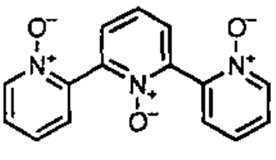

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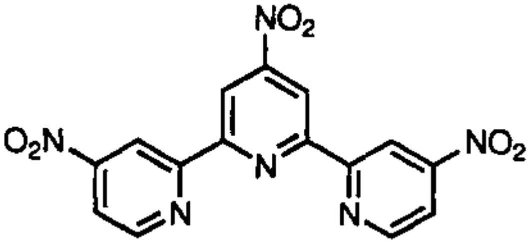
N-Oxidation of a pyridine ring activates it to electrophilic substitution in the 4-position [92]. The three 2,2′:6′,2″-terpyridine-*N*-oxides are therefore useful intermediates in the synthesis of 4-mono-, 4,4″-di- and 4,4′,4″-trisubstituted-2,2′:6′,2″-terpyridines. The resulting substituted *N*-oxides can then be reduced to the corresponding substituted 2,2′:6′,2″-terpyridine [92]. For example, 4,4′,4″-trinitro-2,2′:6′,2″-terpyridine (**11**) is obtained by the treatment of the tri-*N*-oxide with fuming nitric and sulphuric acids, followed by reduction with phosphorus trichloride [92]. Various 4,4′,4″-trisubstituted-2,2′:6′,2″-terpyridines can be obtained from 4,4′,4″-trinitro-2,2′:6′,2″-terpyridine and its tri-*N*-oxide [92]. 2,2′:6′,2″-Terpyridine-1,1″-di-*N*-oxide (**9**) can be reacted with Me_3SiCN followed by benzoyl chloride to give 2,2′:6′,2″-terpyridine-6,6″-dicarbonitrile [46].



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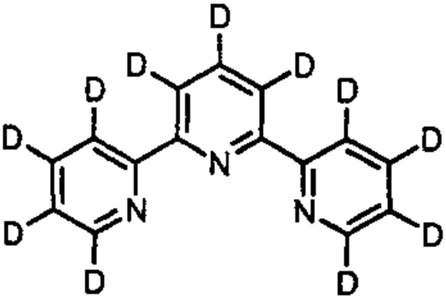
2,2′:6′,2″-Terpyridine-1,1′,1′-tri-*N*-oxide reacts with NaOD in D_2O in a sealed tube at elevated temperature to give the perdeuterio analogue, 2,2′:6′,2″-terpyridine-d_{11}-1,1′,1″-tri-*N*-oxide in 67% yield. The perdeuterio ligand 2,2′:6′,2″-terpyridine-d_{11} (**12**), which can be incorporated into coordination complexes to facilitate interpretation of ^1H NMR spectra, is then obtained by phosphorus trichloride reduction [93].



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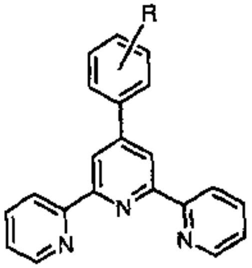
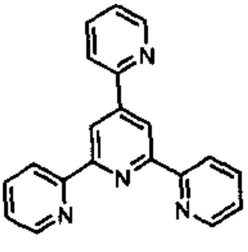
3.2.2. 4′-Aryl-2,2′:6′,2″-terpyridines

4′-Phenyl-2,2′:6′,2″-terpyridine (**2**) and 4′-aryl-2,2′:6′,2″-terpyridines (**13**) are readily obtained from the condensation of benzaldehyde, or the relevant substituted benzaldehyde, with two equivalents of 2-acetylpyridine to give a 1,5-diketone (**5**). This can be isolated prior to aza ring closure and oxidative dehydrogenation, or alternatively, a one-pot process may be used. The diketone 3-phenyl-1,5-bis(2-pyridyl)-1,5-pentanedione is prepared in good yield from benzaldehyde in this manner [77,94]. It exhibits a well-resolved ^1H NMR spectrum, as well as an absorption in its infrared spectrum at 1698 cm^{-1}, which may be assigned to the stretching mode of the conjugated carbonyl groups [77]. Ring closure with hydroxylamine affords **2** in only 8% yield [67], while the use of ammonium acetate in air improves this to 47% [77]. Ligand **2** is also obtained in 10% yield by an analogous one-pot reaction using ammonium acetate in acetamide to achieve ring closure [72].

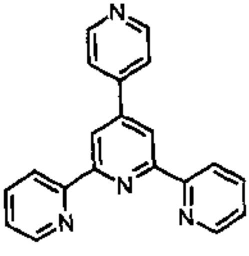
The commercial availability of *para*-substituted benzaldehydes has led to the synthesis of various 4′-(4-substituted-aryl)-2,2′:6′,2″-terpyridines. For example, 4′-(4-methoxyphenyl)-2,2′:6′,2″-terpyridine (**13a**) [72,95], 4′-(4-chlorophenyl)-2,2′:6′,2″-terpyridine (**13b**) [95], 4′-(4-bromophenyl)-2,2′:6′,2″-terpyridine (**13c**) [95], 4′-(4-hydroxyphenyl)-2,2′:6′,2″-terpyridine (**13d**) [95], and 4′-(4-tolyl)-2,2′:6′,2″-terpyridine (or 4′-(4-methylphenyl)-2,2′:6′,2″-terpyridine, **13e**) [95] are obtained in 18–30% yields from the respective aldehydes by this one-pot route. Purification can be achieved by precipitation from acetic acid solution as the hydrobromide salt, which is then redissolved in water. This solution is made basic, resulting in precipitation of the free ligand [95].

Higher yields may, however, be achieved by more strategic methods involving





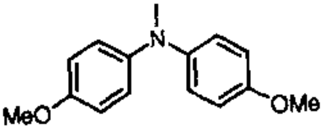
14a



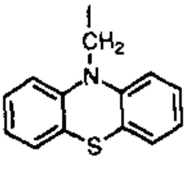
14b

2 R = H
13a R = 4-OMe
13b R = 4-Cl
13c R = 4-Br
13d R = 4-OH
13e R = 4-Me
13f R = 4-NMe_2
13g R = 2,4-$(OMe)_2$
13h R = 3,4-$(OMe)_2$
13i R = 3,4-$(OH)_2$
13j R = 2,5-$(OMe)_2$
13k R = 2,5-$(OH)_2$
13l R = 4-^{t}Bu
13m R = 3-NO_2
13n R = 2-OH
13o R = 4-$CH{=}CH_2$
13p R = 3-NH_2
13q R = 4-NO_2
13r R = 4-($OCH_2C_6H_4NO_2$-3)
13s R = 3-($OCH_2C_6H_4NO_2$-3)
13t R = 4-CH_2Br
13u R = 4-CHO
13v R = 4-$C{\equiv}CH$
13w R = 4-$C{\equiv}CSiMe_3$

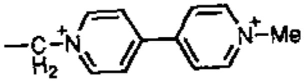
R = 4–



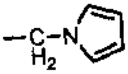
13x



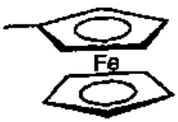
13y



13z



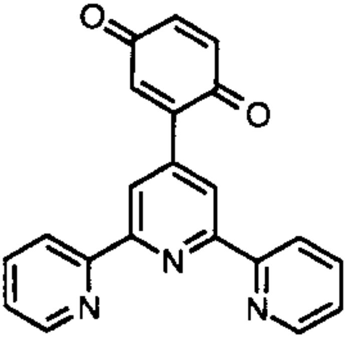
13aa



13bb

isolation of either an enone (**4**) or 1,5-diketone (**5**) intermediate resulting from the condensation of 2-acetylpyridine with the relevant arylaldehyde in basic aqueous ethanol or methanol. Kröhnke has synthesized **13a**, **13b**, **13e**, 4′-(4-(*N*,*N*-dimethylamino)phenyl)-2,2′:6′,2″-terpyridine (**13f**), 4′-(2,4-dimethoxyphenyl)-2,2′:6′,2″-terpyridine (**13g**), and 4′-(2-pyridyl)-2,2′:6′,2″-terpyridine (**14a**), as well as the parent ligand **2**, in good yield via the corresponding enone intermediates [4].

The ligand 4′-(4-hydroxyphenyl)-2,2′:6′,2″-terpyridine (**13d**) can alternatively be prepared (71%) by the hydrolysis of 4′-(4-methoxyphenyl)-2,2′:6′,2″-terpyridine (**13a**) with aqueous hydrogen bromide at reflux in glacial acetic acid [95]. Howard and Ward have prepared 4′-(3,4-dimethoxyphenyl)-2,2′:6′,2″-terpyridine (**13h**) by the Kröhnke route via the enone resulting from the condensation of 2-acetylpyridine with 3,4-dimethoxybenzaldehyde [32]. Hydrolysis with BBr_3 (performed in this case on the ligand coordinated to a ruthenium(II) centre) affords 4′-(3,4-dihydroxyphenyl)-2,2′:6′,2″-terpyridine (**13i**), which possesses a potentially bidentate catechol donor set capable of coordination to a second metal centre [32,33]. Similarly, Colbran and co-workers have prepared 4′-(2,5-dimethoxyphenyl)-2,2′:6′,2″-terpyridine (**13j**) both by one-pot co-condensation of 2,5-dimethoxybenzaldehyde with two equivalents of 2-acetylpyridine in ammonium acetate/acetamide, and alternatively in two steps via the 1,5-diketone. Hydrolysis of free ligand **13j** with concentrated aqueous hydrogen bromide affords the hydroquinonyl ligand 4′-(2,5-dihydroxyphenyl)-2,2′:6′,2″-terpyridine (**13k**), which may be oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone to give 4′-(*p*-quinonyl)-2,2′:6′,2″-terpyridine (**15**). These interconversions may also be performed efficiently on the ligands in situ in their homoleptic $[Fe(L)_2]^{2+}$ complexes [96].



15

4′-(4-t-Butylphenyl)-2,2′:6′,2″-terpyridine (**13l**) can be prepared from 4-*t*-butylbenzaldehyde and 2-acetylpyridine in two steps via the 1,5-diketone intermediate. The introduction of the *t*-butyl group significantly enhances the solubility of the ligand, as well as its complexes, in lipophilic solvents [97]. 4′-(4-Pyridyl)-2,2′:6′,2″-terpyridine (**14b**) can be prepared by isolating the 1,5-diketone intermediate followed by ring closure with ammonium acetate [98,99]. The 1,5-diketone is prepared by the reaction of 4-pyridinecarboxaldehyde with either two equivalents of 2-acetylpyridine in the usual manner [98], or with two equivalents of the morpholine enamine of 2-acetylpyridine, as reported by Thummel and co-workers [99].

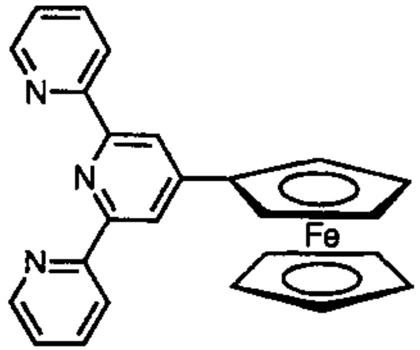
4′-(4-Chlorophenyl)-2,2′:6′,2″-terpyridine (**13b**) [74], 4′-(3-nitrophenyl)-2,2′:6′,2″-terpyridine (**13m**) [100], 4′-(2-hydroxyphenyl)-2,2′:6′,2″-terpyridine (**13n**) [100] and 4′-(4-styrenyl)-2,2′:6′,2″-terpyridine (**13o**) [101] have also been prepared in two stages via the enone intermediates. Reduction of **13m** with hydrazine monohydrate and Raney nickel affords 4′-(3-aminophenyl)-2,2′:6′,2″-terpyridine (**13p**) [100]. Iron(II) and ruthenium(II) bis-ligand complexes of **13n**, **13o** and **13p** may be electropolymerized [100]. A variety of 4′-aryl-2,2′:6′,2″-terpyridines (**13m**, **13q**, **13r**, **13s**) in which the aryl ring bears a *meta* or *para* -nitro or -nitrobenzyloxy substituent have been prepared [45].

The ligand 4′-(4-tolyl)-2,2′:6′,2″-terpyridine (**13e**) can readily be converted to 4′-(4-bromomethylphenyl)-2,2′:6′,2″-terpyridine (**13t**) in 72–90% yield in a photocatalysed reaction with *N*-bromosuccinimide initiated by dibenzoylperoxide in carbon tetrachloride or benzene [18,29,95,102]. 4-{4′-(2,2′:6′,2″-Terpyridinyl)}benzaldehyde (**13u**) can then be obtained (43%) by oxidation of this with excess hexamethylenetetramine at reflux in aqueous ethanol, followed by hydrolysis of the imine intermediate in situ with concentrated hydrochloric acid [29,64]. The author has found that higher yields of pure 4-{4′-(2,2′:6′,2″-terpyridinyl)}benzaldehyde may be obtained, without the need for chromatographic purification, if 2:1 glacial acetic acid–water is used, it being critical that the minimum amount of solvent in which the **13t** is soluble at reflux is used (even slightly larger volumes of solvent result in very significant contamination of the aldehyde by other species). Liang and Schmehl have anchored a 2,2′:6′,2″-terpyridine to a quartz surface by reacting 4′-tolyl-2,2′:6′,2″-terpyridine (**13e**), deprotonated at the methyl group, with a surface-bound bromoalkyl functionality [15].

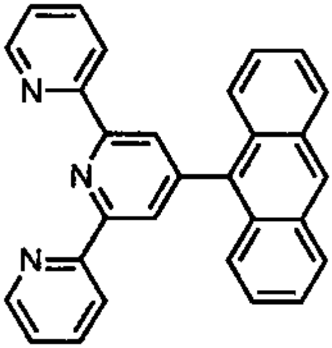
4′-(4-Ethynylphenyl)-2,2′:6′,2″-terpyridine (**13v**) is prepared by deprotection of **13w**, obtained by the reaction of 4′-(4-bromophenyl)-2,2′:6′,2″-terpyridine (**13c**) with trimethylsilylacetylene using [Pd(PPh$_3$)$_2$Cl$_2$] and CuI as catalyst precursors [54].

A study of the effect of covalently-linked electron-donor and -acceptor substituents on ruthenium(II) bis-terpyridine centres has been performed by Collin and co-workers [17,18]. The strongly electron-releasing ligand **13x** can be prepared from the corresponding benzaldehyde. The related ligand **13y** is obtained by the action of phenothiazine on **13t**, while the acceptor-substituted ligand salt [**13z**][NO$_3$]$_2$ is obtained from the reaction of **13t** with a 1-methyl-4,4′-bipyridinium salt. The same group have prepared 4′-(4-pyrrolylmethylphenyl)-2,2′:6′,2″-terpyridine (**13aa**) from pyrrolyl potassium and **13t**, and have electropolymerized a number of its coordination complexes affording metal-functionalized polypyrrole films [102].

Sauvage and co-workers have prepared the ligand 4′-(4-ferrocenylphenyl)-2,2′:6′,2″-terpyridine (**13bb**), which incorporates an electron-releasing ferrocenyl functionality, by the palladium(0) coupling of ferrocenylzinc chloride and 4′-(4-bromophenyl)-2,2′:6′,2″-terpyridine (**13c**) [103]. Constable and co-workers interest in the effect of remote substituents on 2,2′:6′,2″-terpyridine ligands on coordinated metal centres [19,28,98] has led to the preparation of 4′-ferrocenyl-2,2′:6′,2″-terpyridine (**16a**) from ferrocenecarboxaldehyde via both the enone and the 1,5-diketone intermediates. The crystal structure indicates that the ferrocene moiety is rotated by ca. 20° with respect to the central pyridine ring to which it is attached [25]. The groups of Nile and Walsh and of Butler have concurrently conducted similar studies [24,28]. Sauvage and co-workers have synthesized the 4′-porphyrin-substituted 2,2′:6′,2″-terpyridine **17** from 4-{4′-(2,2′:6′,2″-terpyridinyl)}benzaldehyde (**13u**), a dipyrrylmethane and 3,5-di-*t*-butylbenzaldehyde [29,104], and another **18a** from **13u**, pyrrole and 3,5-di-*t*-butylbenzaldehyde [104]. Constable and Smith have prepared 4′-(9-anthryl)-2,2′:6′,2″-terpyridine (**16b**) by a variation on the Kröhnke method. The enone intermediate (prepared from 9-anthraldehyde and 2-acetylpyridine) does not, however, react with the Kröhnke reagent *N*-{1-(2′-pyridyl)-1-oxo-2-ethyl}pyridinium iodide (**6**); the potassium enolate of 2-acetylpyridine is used in the place of this reagent [105].



16a

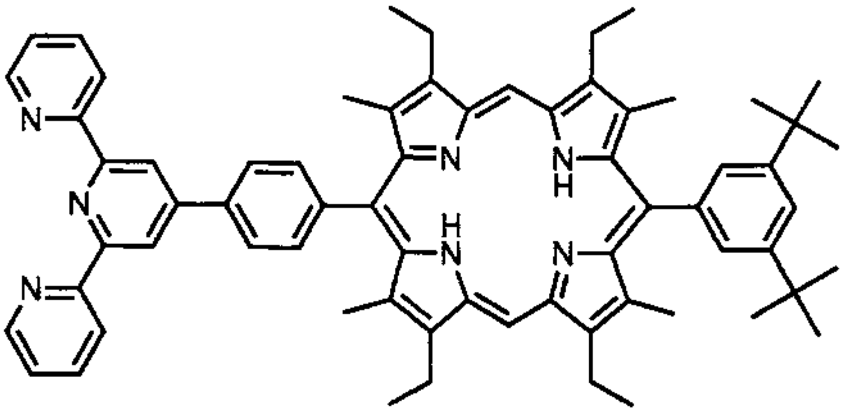


16b

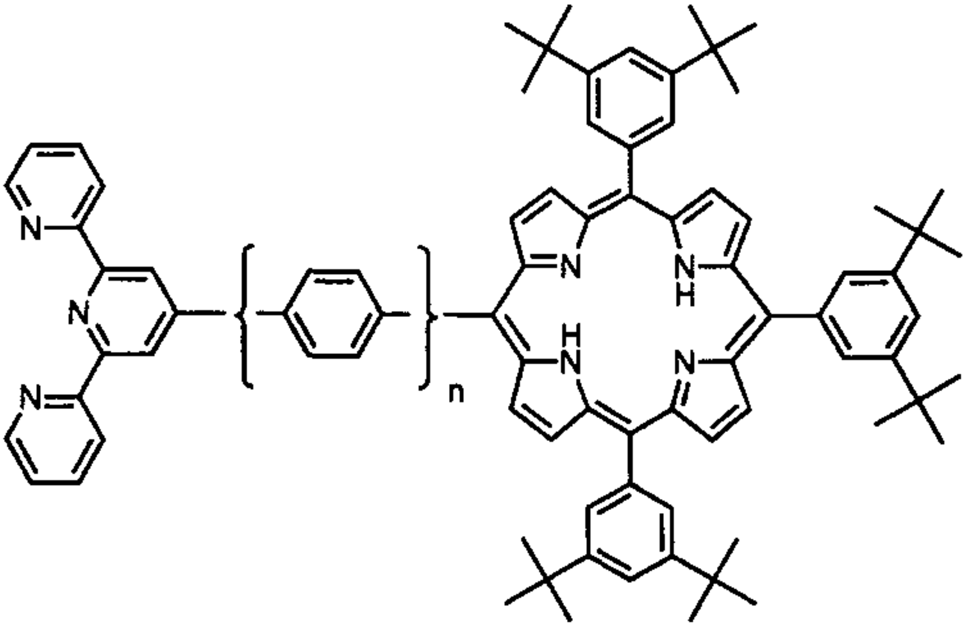
The 4′-(4-substituted-aryl)-2,2′:6′,2″-terpyridines are highly sensitive reagents for the colorimetric determination of iron(II) [4]. For example, the iron(II) complex $[\mathrm{Fe}(\mathbf{13a})_2]^{2+}$ has ϵ 28 000 $\mathrm{dm^3\,mol^{-1}\,cm^{-1}}$ [4,72]. The ligand **13a** [5,6] and a more soluble sulphonic acid derivative [7] have been proposed for the estimation of iron(II) in clinical chemistry. Various studies have also been made of the effect of *para*-methyl and *para*-phenyl substituents on the sensitivity of 2,2′:6′,2″-terpyridine ligands for the determination of iron(II), copper(I), and cobalt(II) [106,107].

3.2.3. 4′-Substituted-2,2′:6′,2″-terpyridines

A wide variety of 4′-substituted-2,2′:6′,2″-terpyridines (**19**) can be prepared for which the substituent group is not aromatic. In general, syntheses rely on applying successive substitution reactions or other functional group interconversions to one of the few 4′-substituted-2,2′:6′,2″-terpyridines, such as 4′-methylthio-2,2′:6′,2″-terpyridine (**7**) and 4′-hydroxy-2,2′:6′,2″-terpyridine (**19a**), which can be prepared directly in good yield. As has already been discussed, non-aromatic substituents tend to be unable to stabilize the enone intermediate (**4**) in the conventional terpyridine synthesis (Scheme 6).

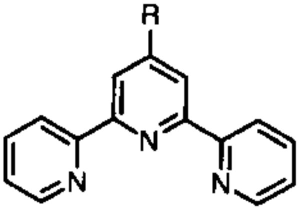


17

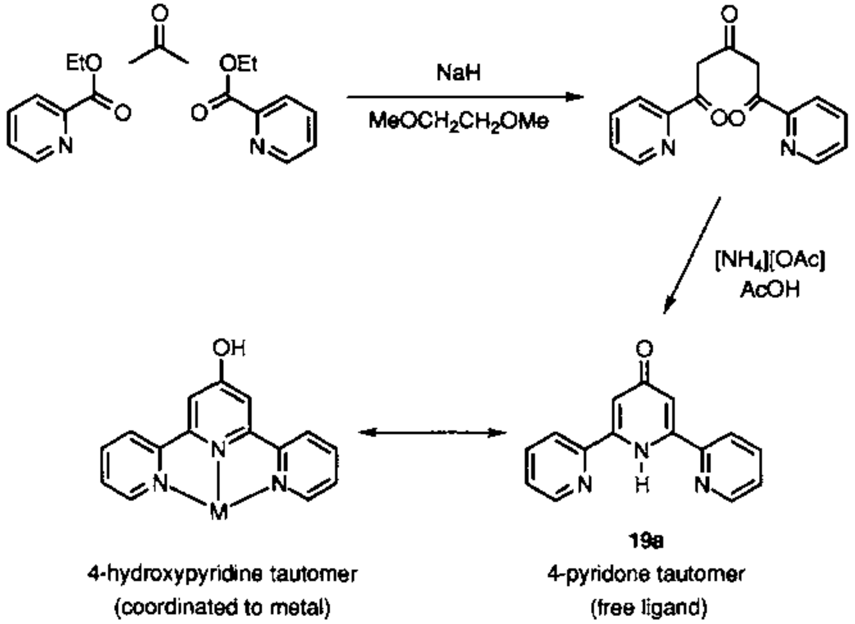


18a n = 1

18b n = 0



7 R = SMe
19a R = OH
19b R = SO_2Me
19c R = Cl
19d R = SO_3CF_3
19e R = NMe_2
19f R = Br
19g R = C≡CH
19h R = $C{\equiv}CSiMe_3$
19i R = C≡CC≡CH
19j R = PO_3Et_2
19k R = PO_3H_2
19l R = CN
19m R = Me
19n R = $C_{19}H_{39}$
19o R = $C_{31}H_{63}$
19p R = $CH_2CH_2C_6H_5$
19q R = CH_2CH_2OMe
19r R = CH_2CH_2OH
19s R = CHO
19t R = $CH{=}CH_2$
19u R = $CH_2CH_2OCH_2C_6H_5$
19v R = $CH_2CH_2CH_2O^tBu$
19w R = $CH_2CH_2CH_2OH$
19x R = $CH_2CH_2CH_2SAc$
19y R = $CH_2CH_2CH_2SS(C_6H_5N\text{-}2)$
19z R = $CH_2CH_2CH_2SSR'$ (R' = peptide)

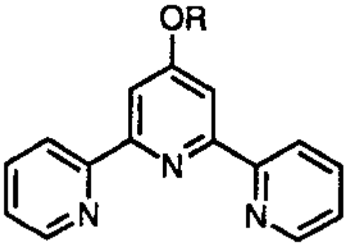


Scheme 11.

4′-Hydroxy-2,2′:6′,2″-terpyridine (or more correctly, 2,2′:6′,2″-terpyridine-4′(1′*H*)-one, **19a**) is prepared in two steps by the Claisen condensation of acetone with excess ethyl picolinate (ethyl 2-pyridinecarboxylate, [67]) to give a 1,3,5-trione (Scheme 11). Ring closure is effected using ammonium acetate to afford the ligand as the pyridone tautomer, 2,2′:6′,2″-terpyridine-4′(1′*H*)-one [51]. The ^{1}H NMR spectrum of the free ligand clearly indicates that the pyridone tautomer is adopted in $CDCl_3$ solution [108]. On coordination to a metal centre, the 4′-hydroxy-2,2′:6′,2″-terpyridine tautomer is obtained.

Potts' synthesis (Scheme 9) of the substitutionally versatile ligand 4′-methylthio-2,2′:6′,2″-terpyridine (**7**), has already been discussed [76,82–84]. Oxidation of **7** by *m*-chloroperbenzoic acid gives 4′-methylsulphonyl-2,2′:6′,2″-terpyridine (**19b**) [76], which can be hydrolysed using hydrogen peroxide [109] or sodium hydroxide [110] in 1,2-dimethoxyethane with a catalytic amount of a crown ether to yield 2,2′:6′,2″-terpyridine-4′(1′*H*)-one (**19a**). Sodium hydroxide can also be used in a variety of polar solvents to convert 4′-halo-, 4′-alkylsulphonyl-, and 4′-arylsulphonyl-2,2′:6′,2″-terpyridines to **19a** [110,111]. 4′-Methylsulphonyl-2,2′:6′,2″-terpyridine (**19b**) reacts with sodium hydride and a wide variety of alcohols, such as hexadecanol and 2-methoxyethanol, to give the corresponding 4′-alkoxy-2,2′:6′,2″-terpyridine (**20**) [112]. The iron(II) complexes of such ligands are of interest as potential thermostable pigments [110–112].

4′-Chloro-2,2′:6′,2″-terpyridine (**19c**) is obtained on treating **19a** with phosphorus pentachloride and phosphorus oxychloride [51], whilst 4′-trifluoromethanesulphonato-2,2′:6′,2″-terpyridine (4′-triflato-2,2′:6′,2″-terpyridine, **19d**) is obtained from the reaction with trifluoromethanesulphonic anhydride [109,113]. 4′-Chloro-2,2′:6′,2″-terpyridine readily reacts with sodium in absolute ethanol to afford 4′-ethoxy-2,2′:6′,2″-terpyridine (**20a**) [19]. The chlorine can be substituted by a wide variety of other alkoxy groups by reaction with the alcohol in dimethylsulphoxide in the presence of potassium hydroxide [114,115]. Newkome and co-workers have used this strategy to attach 2,2′:6′,2″-terpyridine moieties to dendrimers. The individual dendrimers (e.g. **20d**) are built up using peptide-type couplings performed on the 2,2′:6′,2″-terpyridine carboxylic acids (**20b** and **20c**) prepared by linking **19c** to either 1-hydroxybutyric acid or 1-hydroxydodecanoic acid respectively. Two such dendrimers (which need not be identical) may then be linked by the stepwise complexation of their 2,2′:6′,2″-terpyridine functionalities to a ruthenium centre [116].

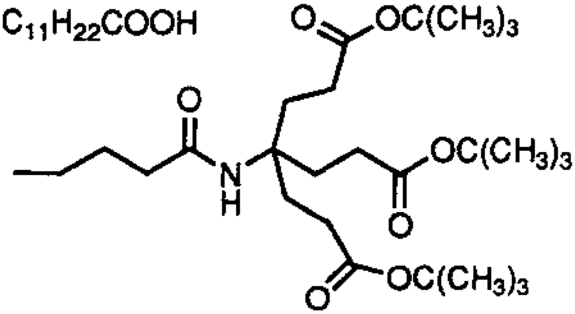


20a R = Et

20b R = C_3H_6COOH

20c R = $C_{11}H_{22}COOH$

20d R =



The iron(II) complex $[Fe(\mathbf{19c})_2]^{2+}$ is cleanly converted to $[Fe(\mathbf{19e})_2]^{2+}$ (**19e** = 4′-(*N*,*N*-dimethylamino)-2,2′:6′,2″-terpyridine) by reaction with dimethylamine at reflux in methanol. The resulting $[Fe(\mathbf{19e})_2]^{2+}$ is oxidatively cleaved using hydrogen peroxide under basic conditions to give free **19e** in 85% yield [19]. No reaction was observed to occur between free **19c** and dimethylamine under a wide variety of conditions [19].

4′-Bromo-2,2′:6′,2″-terpyridine (**19f**) is reputedly obtained by bubbling HBr through a glacial acetic acid solution of **19c** [51]; an alternative method involves bromination of **19a** with $POBr_3$ [16]. 4′-Ethynyl-2,2′:6′,2″-terpyridine (**19g**) is prepared by the deprotection of **19h**, obtained by the reaction of **19d** or **19f** with trimethylsilylacetylene using $[Pd(PPh_3)_2Cl_2]$ and CuI as catalyst precursors [54]. In an iterative manner, 4′-butadiynyl-2,2′:6′,2″-terpyridine (**19i**) may be prepared by the coupling of triethylsilylacetylene bromide with **19g**, followed again by a deprotection step [117].

Diethyl-2,2′:6′,2″-terpyridine-4′-phosphonate (**19j**) is prepared from 4′-bromo-2,2′:6′,2″-terpyridine (**19f**) and diethylphosphite in the presence of a palladium(0) catalyst. The phosphonate functionality can be hydrolysed in situ in a ruthenium complex to give the phosphonic acid derivative (**19k**) which can then be used to anchor the complex to oxide surfaces [16].

Treatment of 4′-methylthio-2,2′:6′,2″-terpyridine (**7**) with potassium cyanide affords 4′-cyano-2,2′:6′,2″-terpyridine (2,2′:6′,2″-terpyridine-4′-carbonitrile, **19l**) [76], whilst treatment with the Grignard reagent methylmagnesium bromide gives 4′-methyl-2,2′:6′,2″-terpyridine (**19m**) [84]. An efficient high yield synthesis of **19m** which may be performed on a multigram scale involves the palladium-catalysed methylation of 4′-triflato-2,2′:6′,2″-terpyridine (**19d**) with $SnMe_4$ [30,31,113]. Two novel methods of preparing **19m** by assembling the central pyridine ring have also been reported. In one procedure, 2-pyridinecarboxaldehyde and 2-(aminomethyl)-pyridine are condensed to give an imine. The imine is deprotonated, giving a 2-aza-allyl anion, which is combined with {2-(iodomethyl)-3-propenyl}trimethylsilane affording a piperidine. This is aromatized with mercuric acetate to **19m** [118]. The other method involves the coupling of a 2-methyleneallyl dianion with two 2-cyanopyridine molecules, thereby constructing the central ring of the terpyridine [119].

The reaction of 4′-methyl-2,2′:6′,2″-terpyridine (**19m**) with lithium diisopropylamide and the appropriate 1-bromoalkane has been used to prepare 4′-nonadecyl-2,2′:6′,2″-terpyridine (**19n**) and 4′-hentriacontyl-2,2′:6′,2″-terpyridine (**19o**). Ruthenium and rhodium complexes of these 4′-alkylated-2,2′:6′,2″-terpyridines have been found to exhibit lyotropic mesomorphism [113]. 4′-(2-Phenylethyl)-2,2′:6′,2″-terpyridine (**19p**) may be prepared from **19m** and benzyl chloride in a similar fashion [45], and reaction of **19m** with lithium 2,2,6,6-tetramethylpiperidide followed by the addition of chloromethyl methyl ether gives 4′-(2-methoxyethyl)-2,2′:6′,2″-terpyridine (**19q**) [84]. 4′-(2-Hydroxyethyl)-2,2′:6′,2″-terpyridine (**19r**) can be synthesized by the reaction of formaldehyde with **19m** [84].

2,2′:6′,2″-Terpyridine-4′-carboxaldehyde (**19s**) can be prepared by the oxidation of 4′-methyl-2,2′:6′,2″-terpyridine (**19m**) with selenium dioxide [84], or else using a mixture of iodine, trifluoroacetic acid and *t*-butyl iodide in dimethylsulphoxide [30,31]. Sauvage and co-workers have prepared the 4′-porphyrin-substituted-2,2′:6′,2″-terpyridine **18b** from **19s** [30,31].

4′-Vinyl-2,2′:6′,2″-terpyridine (**19t**) can be synthesized by a variety of routes [84]. These include the treatment of **19s** with triphenylphosphonium methylide, the treatment of **19q** with potassium *t*-butoxide, dehydration of **19r**, or tosylation of **19r**, followed by elimination of TsOH. The most efficient conversion (36%) of **19m** to **19t** involves the in situ generation, cleavage, and dehydration of 4′-{2-(benzyloxy)ethyl}-2,2′:6′,2″-terpyridine (**19u**) [84]. The treatment of 4′-triflato-2,2′:6′,2″-terpyridine (**19d**) with vinyltributyl tin, triethylamine, and $[Pd(PPh_3)_2Cl_2]$ as a catalyst also gives **19t** [109]. Metal-binding homopolymers and styrene copolymers of **19t** have been synthesized and studied [120].

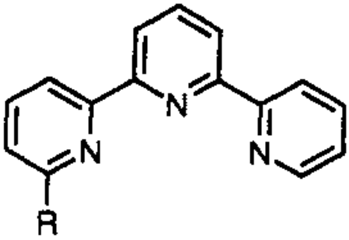
Treatment of 4′-methylthio-2,2′:6′,2″-terpyridine (**7**) with the Grignard reagent derived from the *t*-butyl ether of 3-bromopropanol affords 4′-{3-(*t*-butoxy)propyl}-2,2′:6′,2″-terpyridine (**19v**). Trifluoroacetic acid cleaves this ether to give 4′-(3-hydroxypropyl)-2,2′:6′,2″-terpyridine (**19w**), which can, in turn, be converted to a thiolacetate (**19x**) by thioacetic acid. Hydrolysis of **19x**, followed by in situ reaction with 2-thiopyridine disulphide affords a disulphide **19y**, which can be incorporated as a non-natural functionality into a peptide chain (**19z**) by reaction with a peptide R′SH [121].

3.2.4. Other monosubstituted-2,2′:6′,2″-terpyridines

6-Bromo-2,2′:6′,2″-terpyridine (**21a**) can be obtained in 11% yield by the bromination of 2,2′:6′,2″-terpyridine [62]. Alternatively, **21a** can be prepared more specifically by the Kröhnke method, using *N*-{1-(2′-pyridyl)-1-oxo-2-ethyl}pyridinium iodide (**6**) and the bromo-substituted Mannich base *N*,*N*-dimethyl{3-(6′-bromo-2′-pyridyl)-3-oxopropyl}ammonium chloride [122], or using the bromo-substituted acylpyridinium salt *N*-{1-(6′-bromo-2′-pyridyl)-1-oxo-2-ethyl}pyridinium iodide and the Mannich base *N*,*N*-dimethyl{3-(2′-pyridyl)-3-oxopropyl}ammonium chloride [37]. The action of 6-bromo-2-lithiopyridine on 2,2′-bipyridine also affords **21a** [64].

2-Alkylsulphinylpyridines, generated by the oxidation of the relevant 2-alkylthiopyridine with magnesium monoperoxyphthalate, couple efficiently with 2-pyridyllithium allowing the construction of oligopyridines. As already mentioned, 2,2′:6′,2″-terpyridine can be prepared from 6-ethylthio-2,2′-bipyridine in this manner (Scheme 2) [34], and 6-bromo-2,2′:6′,2″-terpyridine (**21a**) and 6-methyl-2,2′:6′,2″-terpyridine (**21b**) may also be prepared [123]. The same group have prepared a chiral 2,2′:6′,2″-terpyridine (**21c**) by coupling a chirally 6-substituted-2-bromopyridine with 6-ethylsulphinyl-2,2′-bipyridine, and are currently preparing other chiral oligopyridines [13]. 6-Ethylthio-2,2′:6′,2″-terpyridine (**21d**) is prepared in high yield from 6,6′-bis(ethylthio)-2,2′-bipyridine and 2-pyridyllithium. 6-Bromomethyl-2,2′:6′,2″-terpyridine (**21e**) is prepared in 45% yield in a similar manner, utilizing a protected equivalent of 6-bromomethyl-2-lithiopyridine, which is deprotected after coupling [34]. 6-Bromomethyl-2,2′:6′,2″-terpyridine (**21e**) may alternatively be prepared by the radical bromination of **21b** with *N*-bromosuccinimide [123], or else 6-bromo-2,2′:6′,2″-terpyridine (**21a**) may be converted to 6-hydroxymethyl-2,2′:6′,2″-terpyridine (**21f**), which reacts with carbon tetrabromide and triphenylphosphine to give **21e** [123].

Desulphurization of 4-methyl-4′-methylthio-2,2′:6′,2″-terpyridine (**27a**) or 6-methyl-4′-methylthio-2,2′:6′,2″-terpyridine (**28a**), prepared by Potts' methodology, affords 4-methyl-2,2′:6′,2″-terpyridine (**22a**) and **21b** respectively [84]. 6-Methyl-2,2′:6′,2″-terpyridine (**21b**) can also be obtained in low yield by the palla-



21a $R = Br$

21b $R = Me$

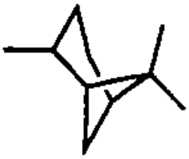
21c $R = CHMeOSi{}^{t}BuMe_2$

21d $R = SEt$

21e $R = CH_2Br$

21f $R = CH_2OH$

21g R =



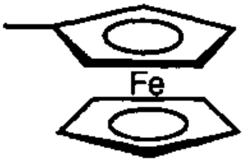
21h $R = CHO$

21i $R = CH_2CH_2OMe$

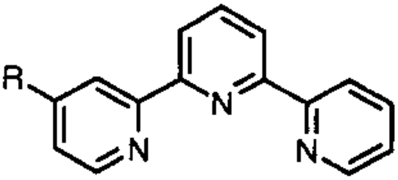
21j $R = CH_2CH_2OH$

21k $R = CH{=}CH_2$

21l R =



dium-on-carbon coupling [124] of 2,2′-bipyridine and 2-methylpyridine (α-picoline) [125]. Hamilton and co-workers have prepared 5-methyl-2,2′:6′,2″-terpyridine (**23a**) from 2-acetyl-5-picoline by Jameson's method, and have converted this to a 5-thiourea-functionalized-2,2′:6′,2″-terpyridine (**23b**). When two such ligands are coordinated to a ruthenium(II) centre, the two thiourea moieties are oriented so as to provide a well ordered recognition site for dicarboxylate anions such as glutarate [88]. Jameson's method has also been used to prepare chiral 6-(6,6-dimethylnorpynan-2-yl)-2,2′:6′,2″-terpyridine (**21g**), from 2-acetyl-6-(6,6-dimethylnorpynan-2-yl)pyridine, for use in enantioselective reactions [12]. The methyl substituent of **21b** and **22a** can be converted to carboxaldehyde (**21h**, **22b**), 2-methoxyethyl (**21i**, **22c**), 2-hydroxyethyl (**21j**, **22d**), or vinyl (**21k**, **22e**) functionalities by the routes used for 4′-methyl-2,2′:6′,2″-terpyridine (**19m**) [84].

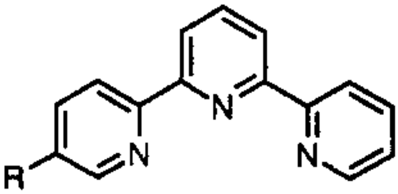


22a R = Me
22b R = CHO
22c R = CH_2CH_2OMe
22d R = CH_2CH_2OH
22e R = $CH{=}CH_2$

Butler and co-workers have prepared both 6-ferrocenyl-2,2′:6′,2″-terpyridine (**21l**) [23] and 3′-ferrocenyl-2,2′:6′,2″-terpyridine (**24**) [22] by the coupling of ferrocenyllithium with 2,2′:6′,2″-terpyridine.

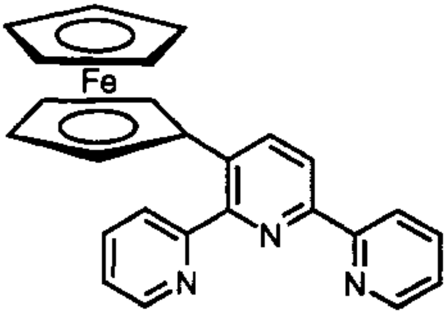
3.2.5. Symmetrically disubstituted-2,2′:6′,2″-terpyridines

The activation of the carbon ortho to the nitrogen in a pyridine ring to attack by aryllithium species [64] allows 6,6″-diphenyl-2,2′:6′,2″-terpyridine (**25a**) to be prepared by the action of phenyllithium on 2,2′:6′,2″-terpyridine [126]. 6,6″-Dibromo-2,2′:6′,2″-terpyridine (**25b**) can be prepared by the bromination of 2,2′:6′,2″-terpyridine, with 6-bromo-2,2′:6′,2″-terpyridine (**21a**) also being produced in this reaction [62]. Alternatively, Kröhnke-type routes utilizing 6-bromo-2-acetylpyridine [21] afford **25b** in higher yield [37,39], as does ammonium acetate ring closure of the diketone 1,5-bis(6-bromo-2-pyridyl)-pentane-1,5-dione prepared by Owsley's reaction (Scheme 7) of 6-bromo-2-lithiopyridine and *N*,*N*,*N*′,*N*′-tetramethylglutaramide ($Me_2NCO(CH_2)_3CONMe_2$) [75]. An efficient, novel, one-pot synthesis of **25b** involves the lithiation of 2,6-dibromopyridine with four equivalents of butyllithium,



23a R = Me

23b R = $CH_2NHC(S)NHBu$



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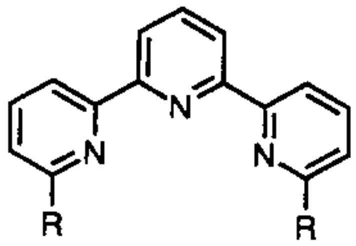
followed by treatment with phosphorus trichloride [127]. 6,6″-Dibromo-2,2′:6′,2″-terpyridine can also be obtained by the desulphurization of 6,6″-dibromo-4′-methylthio-2,2′:6′,2″-terpyridine (**30h**) synthesized by Potts' route [83]. The reaction of **25b** with methylhydrazine affords the pentadentate ligand 6,6″-bis-(methylhydrazino)-2,2′:6′,2″-terpyridine (**25c**) [39].

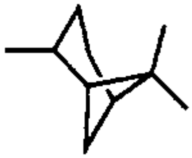
6-Methyl-2-pyridinecarboxaldehyde reacts with 1,3-propanedithiol to give the corresponding dithiane, in which the carbonyl group has been protected. Reaction with 1,3-dilithiopropane links two of these moieties, giving a 1,5-bis-dithiane. Deprotection with mercury(II) affords 1,5-bis(6-methyl-2-pyridyl)-pentane-1,5-dione, which undergoes ring closure by hydrazine hydrochloride to give 6,6″-dimethyl-2,2′:6′,2″-terpyridine (**25d**) in 35% overall yield [38]. 6,6″-Dimethyl-2,2′:6′,2″-terpyridine can also be prepared in 15% overall yield by the pyrolysis of the *N*,*N*,*N*-trimethylhydrazonium tetrafluoroborate obtained from 6-methyl-2-acetylpyridine [128].

Sauvage and Ward have prepared 5,5″-bis(4-methoxyphenyl)-2,2′:6′,2″-terpyridine (**26a**) from 2-acetyl-5-(4-methoxyphenyl)pyridine by Potts' methodology [87]. Sauvage's group have prepared 5,5″-dimethyl-2,2′:6′,2″-terpyridine (**26b**) from 2-acetyl-5-picoline by Jameson's route, and in several steps (**26c–f**) converted it to 5,5″-bis(3-bromopropyl)-2,2′:6′,2″-terpyridine (**26g**) [44]. Jameson's method has also been used to prepare chiral 6,6′-bis-(6,6-dimethylnorpynan-2-yl)-2,2′:6′,2″-terpyridine (**25e**), from 2-acetyl-6-(6,6-dimethylnorpynan-2-yl)pyridine, for use in enantioselective reactions [12].



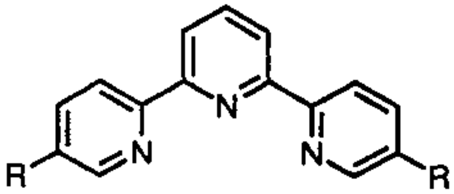
25a R = Ph
25b R = Br
25c R = $NMeNH_2$
25d R = Me

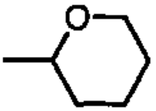
25e R =



25f R = 2-pyridyl
25g R = 2-C_6H_4OMe
25h R = 2-C_6H_4OH
25i R = S^tBu
25j R = CN
25k R = CH_2NH_2
25l R = $CH_2N(CH_2COO^tBu)_2$
25m R = $CH_2N(CH_2COOH)_2$

Desulphurization of 4,4″-bis(alkylthio)-6,6″-diphenyl-2,2′:6′,2″-terpyridines prepared by an extension of Potts' method afford **25a**. 2,2′:6′,2″:6″,2‴:6‴,2⁗-Quinquepyridine (**25f**) may be prepared from 3,3′-bis(methylthio)-1-(2-pyridyl)-propen-1-one and 2,6-diacetylpyridine in a similar manner [76]. Both 6,6″-diphenyl-2,2′:6′,2″-terpyridine (**25a**) [129] and 6,6″-bis(2-methoxyphenyl)-2,2′:6′,2″-terpyridine (**25g**) [89] have been prepared by using a Kröhnke-type method to assemble the two outer pyridine rings of the 2,2′:6′,2″-terpyridine moiety. The potentially pentadentate heterofunctional ligand 6,6″-bis(2-hydroxyphenyl)-2,2′:6′,2″-terpyridine (**25h**) is obtained by demethylation of **25g** using molten pyridine hydrochloride [89].



26a $R = 4\text{-}C_6H_4OMe$
26b $R = Me$
26c $R = CH_2Li$
26d $R = (CH_2)_3OR'$; $R' =$ 
26e $R = (CH_2)_3OH$
26f $R = (CH_2)_3OSO_2Me$
26g $R = (CH_2)_3Br$
26h $R = NO_2$
26i $R = 4\text{-}C_6H_4OH$

Tohda et al. have synthesized the strongly π-accepting ligand 5,5″-dinitro-2,2′:6′,2″-terpyridine (**26h**) by assembling the two terminal rings of the 2,2′:6′,2″-terpyridine in a ring transformation reaction of 1-methyl-3,5-dinitropyrid-2-one with 2,6-diacetylpyridine in the presence of ammonia [130].

Tiecco et al. have isolated small quantities of 6,6″-bis(*t*-butylthio)-2,2′:6′,2″-terpyridine (**25i**) as a by-product of the nickel(0) homo-coupling reaction of 2-bromo-6-(*t*-butylthio)pyridine [131].

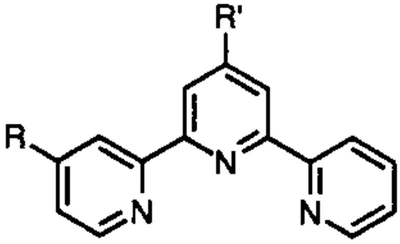
Mukkala and Takalo have used the reaction of 2,2′:6′,2″-terpyridine-1,1″-di-*N*-oxide (**9**) with Me_3SiCN followed by benzoyl chloride to obtain 2,2′:6′,2″-terpyridine-6,6″-dicarbonitrile (**25j**). Reduction with borane–tetrahydrofuran complex gives 6,6″-bis(aminomethyl)-2,2′:6′,2″-terpyridine (**25k**). Reaction of **25k** with *t*-butylbromoacetate affords the tetra-acetate **25l** which after hydrolysis with trifluoroacetic acid gives the polydentate tetrakis(acetic acid) ligand **25m** suitable for chelating lanthanide(III) ions [46].

3.2.6. Asymmetrically disubstituted-2,2′:6′,2″-terpyridines

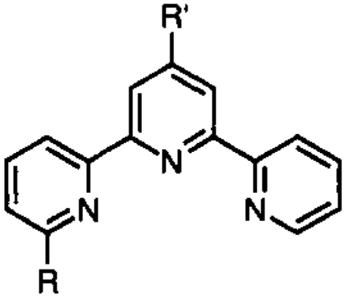
Potts' method can be used to obtain 4-methyl-4′-methylthio-2,2′:6′,2″-terpyridine (**27a**) and 6-methyl-4′-methylthio-2,2′:6′,2″-terpyridine (**28a**) by reaction of the potassium enolate of the appropriate methyl-2-acetylpyridine with the usual α-oxoketene dithioacetal [84]. 6-Acetyl-4′-(*n*-propylthio)-2,2′:6′,2″-terpyridine (**28b**), a useful intermediate in the synthesis of the higher oligopyridines, has been prepared by the acid-catalysed hydration of 6-ethynyl-4′-(*n*-propylthio)-2,2′:6′,2″-terpyridine (**28c**). The alkyne **28c** was obtained after deprotection of **28d**, prepared by the reaction of 6-bromo-4′-(*n*-propylthio)-2,2′:6′,2″-terpyridine (**28e**) with 2-methyl-3-butyn-2-ol. The 6-bromo-4′-(*n*-propylthio)-2,2′:6′,2″-terpyridine was prepared using a modification of the usual method from the α-oxoketene dithioacetal 3,3′-bis(*n*-propylthio)-1-(2-pyridyl)propen-1-one and 6-bromo-2-acetylpyridine [132]. The reaction of **28a** with potassium *t*-butoxide in *N*,*N*-dimethylformamide in the presence of air affords both 4′-methylthio-2,2′:6′,2″-terpyridine-6-carboxylic acid (**28f**, 40%) and 6-(*N*,*N*-dimethylamido)-4′-methylthio-2,2′:6′,2″-terpyridine (**28g**, 9%), which are readily separated owing to the differences in their solubilities [132]. 6-Acetyl-4′-methylthio-2,2′:6′,2″-terpyridine (**28h**) can be obtained from carboxylic acid **28f** in three steps. The carboxylic acid is first converted to the corresponding ethyl ester (**28i**), which is then reacted with ethyl acetate to afford the 6-ethoxymalonyl derivative (**28j**). The ethoxymalonyl group is then hydrolysed with aqueous HCl to give **28h** [132].

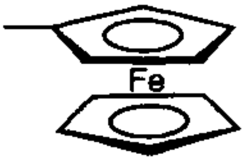
6-Bromo-4′-ferrocenyl-2,2′:6′,2″-terpyridine (**28k**) has been prepared by the Kröhnke route via the enone derived from 6-bromo-2-acetylpyridine and ferrocenecarboxaldehyde; two equivalents of this ligand may be coupled using a nickel(0) catalyst to give 4′,4′′′′-di(ferrocenyl)-2,2′:6′,2″:6″,2‴:6‴,2′′′′:6′′′′,2′′′′′-sexipyridine [27].

4,4′-Diphenyl-2,2′:6′,2″-terpyridine (**27b**) has been prepared in low yield by McMillin and co-workers by the coupling of 4,4′-diphenyl-2,2′-bipyridine and 2-bromopyridine [133].



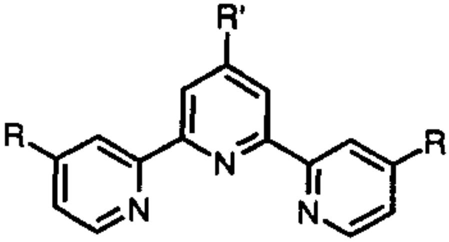
	R	**R'**
27a	Me	SMe
27b	Ph	Ph



	R	R′
28a	Me	SMe
28b	$COCH_3$	$SCH_2CH_2CH_3$
28c	C≡CH	$SCH_2CH_2CH_3$
28d	$C{\equiv}CMe_2OH$	$SCH_2CH_2CH_3$
28e	Br	$SCH_2CH_2CH_3$
28f	COOH	SMe
28g	$CONMe_2$	SMe
28h	COMe	SMe
28i	COOEt	SMe
28j	$COCH_2COOEt$	SMe
28k	Br	

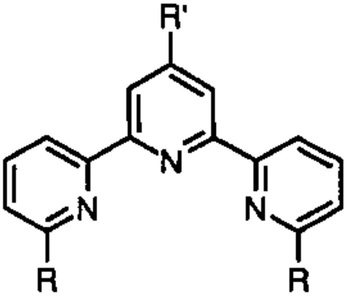
3.2.7. *Symmetrically polysubstituted-2,2′:6′,2″-terpyridines*

4,4″-Disubstituted- and 6,6″-disubstituted-4′-aryl-2,2′:6′,2″-terpyridines (**29** and **30**, R′=aryl) can be prepared by the reaction of the relevant 4- or 6-substituted 2-acetylpyridine with the desired benzaldehyde. The one-pot co-condensation of 2.2 equivalents of 4-phenyl-2-acetylpyridine with benzaldehyde in a sealed tube affords 4,4′,4″-triphenyl-2,2′:6′,2″-terpyridine (**29a**, terosite) in 21% yield [85]. Various Kröhnke-type syntheses have also been reported, offering a concomitant increase in yield [86,134]. 4,4′,4″-Triphenyl-2,2′:6′,2″-terpyridine is used extensively as a sensitive reagent for the determination of iron [106], for example in blood serum [8–11], on account of the high extinction coefficient of $[\mathrm{Fe}(\mathbf{29a})_2]^{2+}$ (ϵ 28 500 dm^3 mol^{-1} cm^{-1}) compared with those for the analogous complexes $[\mathrm{Fe}(\mathbf{1})_2]^{2+}$ (ϵ 11 900 dm^3 mol^{-1} cm^{-1}) and $[\mathrm{Fe}(\mathbf{2})_2]^{2+}$ (ϵ 22 600 dm^3 mol^{-1} cm^{-1}) with less highly conjugated ligands [135]. 4,4″-Dimethyl- (**29b**, terosole) [85], 4,4″-diethyl- (**29c**) [85] and 4,4″-di-*n*-pentyl-4′-phenyl-2,2′:6′,2″-terpyridine (**29d**) [72] have all been prepared in this way, as have 6,4′,6″-triphenyl-2,2′:6′,2″-terpyridine (**30a**) [85] and 4,4″,6,6″-tetramethyl-4′-phenyl-2,2′:6′,2″-terpyridine (**31**) [72].

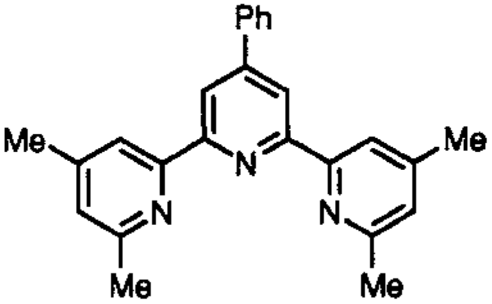


	R	R'
11	NO_2	NO_2
29a	Ph	Ph
29b	Me	Ph
29c	Et	Ph
29d	$(CH_2)_4CH_3$	Ph
29e	NH_2	NH_2
29f	OMe	OMe
29g	OEt	OEt
29h	Cl	Cl
29i	Me	Me
29j	Et	Et
29k	^{i}Pr	^{i}Pr
29l	^{n}Bu	^{n}Bu
29m	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$
29n	^{t}Bu	^{t}Bu

The reaction of 6-bromo-2-acetylpyridine with benzaldehyde under a variety of stoichiometries and conditions affords an enone rather than a diketone. Reaction of this enone with the bromo-substituted acylpyridinium salt *N*-{1-(6′-bromo-2′-pyri-



	R	R'
30a	Ph	Ph
30b	Br	Ph
30c	$C\equiv CSiMe_3$	Ph
30d	$C\equiv CH$	Ph
30e	PPh_2	Ph
30f	$NMeNH_2$	Ph
30g	Cl	Cl
30h	Br	SMe
30i	$CH_2N(CH_2COOH)_2$	$C_6H_3(NH_2\text{-}3)(OMe\text{-}4)$
30j	$CH_2N(CH_2COOH)_2$	$C_6H_3(NCS\text{-}3)(OMe\text{-}4)$



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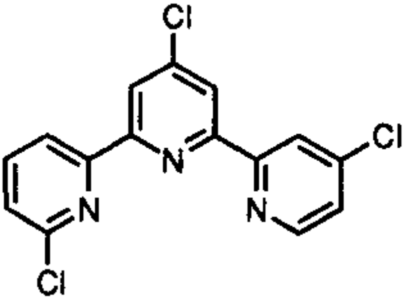
dyl)-1-oxo-2-ethyl}pyridinium iodide affords 6,6″-dibromo-4′-phenyl-2,2′:6′,2″-terpyridine (**30b**) in high yield [36]. 6,6″-Dibromo-4′-phenyl-2,2′:6′,2″-terpyridine is a useful starting material for the synthesis of a variety of macrocyclic and multifunctional ligands. It reacts with trimethylsilylacetylene to afford 6,6″-bis(trimethylsilylethynyl)-4′-phenyl-2,2′:6′,2″-terpyridine (**30c**), which can be deprotected to give 6,6″-bis(ethynyl)-4′-phenyl-2,2′:6′,2″-terpyridine (**30d**) [136]. The heterobifunctional ligand 6,6″-bis(diphenylphosphino)-4′-phenyl-2,2′:6′,2″-terpyridine (**30e**) can be prepared by the action of lithium diphenylphosphide on **30b** [137]. The pentadentate ligand 6,6″-bis(methylhydrazino)-4′-phenyl-2,2′:6′,2″-terpyridine (**30f**) is obtained in 89% yield by the action of *N*-methylhydrazine on **30b** [36]. It is of note that placing alkyl or aryl substituents in both of the 6- and 6″-positions of a 2,2′:6′,2″-terpyridine prevents coordination to an iron(II) centre on steric grounds [62,106], though coordination to a ruthenium(II) centre can be achieved [138].

A convenient route to the 4,4′,4″-trisubstituted-2,2′:6′,2″-terpyridines is to perform substitution reactions on 2,2′:6′,2″-terpyridine-1,1′,1″-tri-*N*-oxide (see Section 3.2.1). 4,4′,4″-Trinitro-2,2′:6′,2″-terpyridine (**11**) is obtained by the treatment of 2,2′:6′,2″-terpyridine-1,1′,1″-tri-*N*-oxide with fuming nitric and sulphuric acids, followed by reduction by phosphorus trichloride [92]. The 4,4′,4″-trinitro-2,2′:6′,2″-terpyridine-1,1′,1″-tri-*N*-oxide can be reduced using acetic anhydride and a palladium catalyst to afford 4,4′,4″-triamino-2,2′:6′,2″-terpyridine (**29e**) [92]. Treatment of **11** with sodium methoxide or sodium ethoxide gives 4,4′,4″-trimethoxy-2,2′:6′,2″-terpyridine (**29f**) and 4,4′,4″-triethoxy-2,2′:6′,2″-terpyridine (**29g**) respectively, while treatment with ethanoyl chloride affords 4,4′,4″-trichloro-2,2′:6′,2″-terpyridine (**29h**) [92]. Direct reaction of 2,2′:6′,2″-terpyridine-1,1′,1″-tri-*N*-oxide (**10**) with phosphorus oxychloride affords 6,4′,6″-trichloro-2,2′:6′,2″-terpyridine (**30g**) and 6,4′,4″-trichloro-2,2′:6′,2″-terpyridine (**32**) [37].



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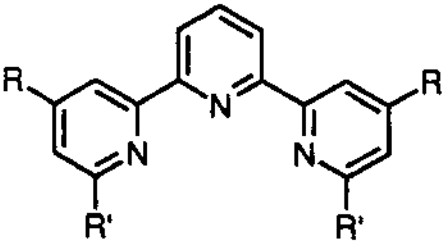
4,4′,4″-Trialkyl-2,2′:6′,2″-terpyridines can be obtained by the palladium-on-carbon catalysed dehydrogenative coupling of the corresponding 4-substituted pyridine. 4,4′,4″-Trimethyl- (**29i**), 4,4′,4″-triethyl- (**29j**), 4,4′,4″-tri-iso-propyl- (**29k**), 4,4′,4″-tri-*n*-butyl- (**29l**), and 4,4′,4″-tri-*n*-pentyl-2,2′:6′,2″-terpyridine (**29m**) have all been prepared in low yield in this way [124]. 4,4′,4″-Tri-*t*-butyl-2,2′:6′,2″-terpyridine (**29n**) can be prepared in 35–50% yield by the palladium-on-carbon coupling of 4-(*t*-butyl)pyridine on a multigram scale [139,140].

Potts' route has been used to prepare 6,6″-dibromo-4′-methylthio-2,2′:6′,2″-terpyridine (**30h**) [83]. By an extension of this methodology, 4,4″-bis(methylthio)-6,6″-diphenyl-2,2′:6′,2″-terpyridine (**33a**) can be prepared by the reaction of the α-oxoketene dithioacetal of benzene with the bis-enolate of 2,6-diacetylpyridine to afford a tetra-ketone, followed by ring closure using ammonium acetate in glacial acetic acid [76]. Alternatively, the bis-α-oxoketene bis(methylthio)acetal or bis(*n*-propylthio)-acetal of 2,6-diacetylpyridine can be reacted with two equivalents of the potassium enolate of acetophenone, giving the 4,4″-bis(alkylthio)-6,6″-diphenyl-2,2′:6′,2″-terpyridines **33a** and **33b** in ca. 50% yield [90].

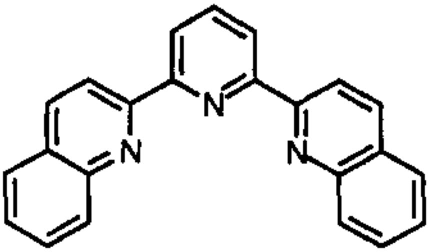


	R	R'
33a	SMe	Ph
33b	$SCH_2CH_2CH_3$	Ph
33c	Ph	$COO^- NH_4^+$
33d	Ph	COOH
33e	Ph	COOMe
33f	Ph	CH_2OH
33g	Ph	CH_2Br
33h	Ph	$CH_2N(CH_2COOH)_2$
33i	Ph	$CH_2N(CH_2COO^tBu)_2$

Mukkala et al. have prepared diammonium 4,4″-diphenyl-2,2′:6′,2″-terpyridine-6,6″-dicarboxylate (**33c**) by assembling the two terminal rings of the terpyridine by a Kröhnke-type methodology from the bis-pyridinium iodide of 2,6-diacetylpyridine and two equivalents of the necessary enone, with the ring closure being performed using ammonium acetate [45]. Functional group interconversions afford the diacid **33d**, bis(methylester) **33e**, 4,4″-diphenyl-6,6″-bis(hydroxymethyl)-2,2′:6′,2″-terpyridine (**33f**) and 4,4″-diphenyl-6,6″-bis(bromomethyl)-2,2′:6′,2″-

terpyridine (**33g**) ligands in turn. 4,4″-diphenyl-6,6″-bis(bromomethyl)-2,2′:6′,2″-terpyridine was converted to the tetrakis(acetic acid) **33h** in two steps via the tetra-ester **33i** [45]. They have also used the same functional group interconversions as used to convert 2,2′:6′,2″-terpyridine-1,1″-di-*N*-oxide (**9**) into a tetrakis(acetic acid) ligand **25m** to convert 4′-substituted-terpyridines **2**, **13m**, **13q**, **13r**, **13s** and **19p** into tetrakis(acetic acid) ligands. A number of functional group interconversions performed on the 4′-substituents allow the europium(III) and terbium(III) complexes to be coupled to proteins as luminescent labels [45,47].

The benzo-disubstituted 2,2′:6′,2″-terpyridine analogue 2,6-di(2′-quinolyl)pyridine (**34**) is obtained, along with 2-acetyl-6-(2′-quinolyl)pyridine, from the condensation of 2-aminobenzaldehyde with 2,6-diacetylpyridine. Benzo-substitution renders this ligand more sterically demanding than 2,2′:6′,2″-terpyridine with the result that $[Fe(\mathbf{34})_2]^{2+}$ is high spin, in contrast to $[Fe(tpy)_2]^{2+}$ having a low spin configuration [141].



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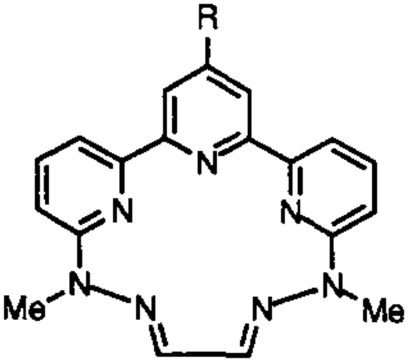
4. 2,2′:6′,2″-Terpyridine ligands incorporating other metal binding groups

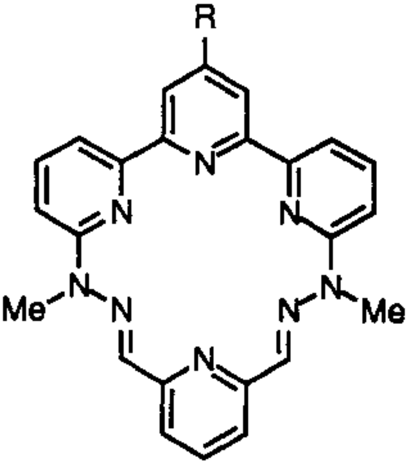
The strong affinity of 2,2′:6′,2″-terpyridine for metal binding makes it an ideal functionality for incorporating into macrocyclic and other polyfunctional ligands designed, often specifically, to coordinate one or more metal ions.

Template reactions of transition metal complexes of the pentadentate ligand 6,6″-bis(methylhydrazino)-4′-phenyl-2,2′:6′,2″-terpyridine (**30f**) [36,40] with ethanedial result in the formation of complexes containing a pentadentate N_5 macrocyclic ligand (**35a**). The ligands 6,6″-bis(methylhydrazino)-2,2′:6′,2″-terpyridine (**25c**) and 6,6″-bis(methylhydrazino)-4′-phenyl-2,2′:6′,2″-terpyridine (**30f**) both undergo transient template reactions with ethanedial in the presence of dimethyltin(IV). The free N_5 macrocycles (**35a**, **35b**) are isolated rather than the complexes, due to the mismatch in size between the metal and the cavity of the macrocycle preventing complex formation [39,41,42]. The same ligands **25c** and **30f** react with nickel(II) acetate and 2,6-pyridinedialdehyde to give hexadentate N_6 macrocycles **36a** and **36b** respectively [43].

Reaction of 5,5″-bis(3-bromopropyl)-2,2′:6′,2″-terpyridine (**26g**) with 2,9-bis-(4-hydroxyphenyl)-1,10-phenanthroline in the presence of Cs_2CO_3 affords a



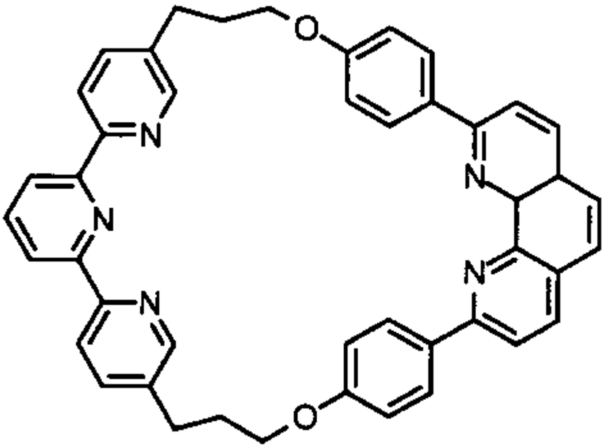
35a R = Ph
35b R = H



36a R = H
36b R = Ph

macrocyclic ligand (37) containing both a terdentate and a bidentate metal binding domain. When this ligand is incorporated in a copper catenate the copper binds to the tridentate 2,2′:6′,2″-terpyridine binding site when in the +II oxidation state, and to the bidentate 2,2′-bipyridine site when in the +I state. The mode of binding may, therefore, be controlled electrochemically [44].

Newkome and co-workers have prepared a variety of polyether macrocycles incorporating 2,2′:6′,2″-terpyridine functionalities. They have found that the macrocyclization step is best performed on the more flexible substituted



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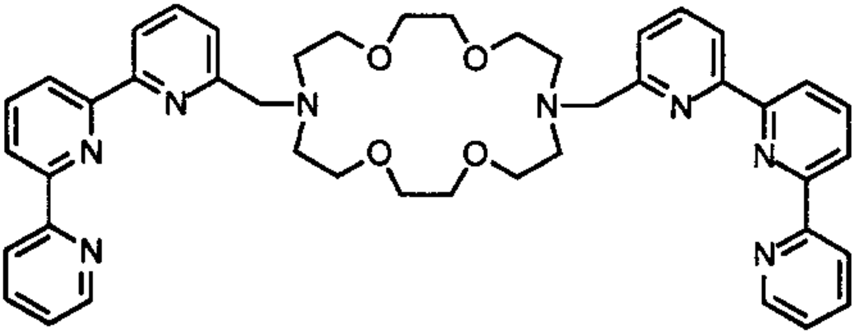
bis(2-pyridine)-1,5-propanedione before the aza ring closure step in which the rigid 2,2′:6′,2″-terpyridine functionality is formed [37,38].

Tanaka and co-workers have prepared pendant arm macrocycle **38** by attaching two 6-bromomethyl-2,2′:6′,2″-terpyridine (**21e**) functionalities to a diaza-18-crown ether with a view to tailoring the selective binding of specific metal ions [34,35]. The heterobifunctional ligand 6,6″-bis(diphenylphosphino)-4′-phenyl-2,2′:6′,2″-terpyridine (**30e**) can coordinate to rhodium(I) centres via the phosphorus atoms giving a 2:2 complex containing two non-coordinated 2,2′:6′,2″-terpyridine functionalities, which are available to bind other metal centres [137].



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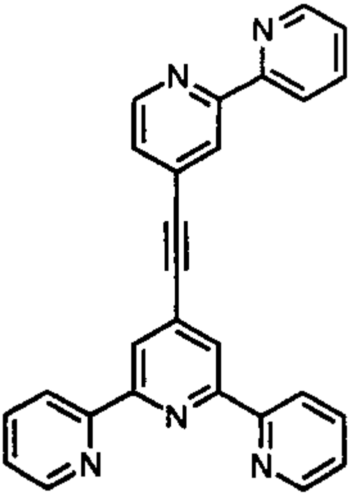
Mukkala and co-workers' tetrakis(acetic acid)-2,2′:6′,2″-terpyridine ligands, e.g. **25m**, are extremely effective chelates for europium(III), terbium(III) and dysprosium(III), giving luminescent complexes [45–47]. Further functionalization of additional 4′-substituents allows these chelates to be attached to proteins as luminescent markers [45]. Similarly, a group at Stirling Winthrop have prepared the 4′-(3-amino-4-methoxyphenyl) analogue **30i**, and have converted the amino functionality to isothiocyanate (**30j**), allowing oligonucleotides to be attached [48].

Ziessel and co-workers have prepared **39** incorporating separate 2,2′-bipyridine and 2,2′:6′,2″-terpyridine functionalities by the efficient palladium(0)-catalysed cross-coupling of 4′-triflato-2,2′:6′,2″-terpyridine (**19d**) with 4′-ethynyl-2,2′-bipyridine [142,143].



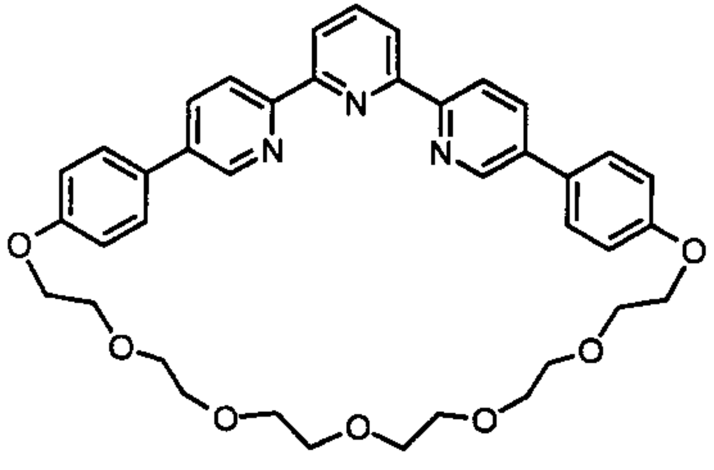
39

After coordination of two 5,5″-bis(4-methoxyphenyl)-2,2′:6′,2″-terpyridine (**26a**) ligands to a ruthenium(II) centre, the methoxy groups can be deprotected giving the complex $[Ru(\mathbf{26i})_2]^{2+}$. The two phenol groups of each ligand **26i** undergo a cyclization reaction with the diiodo derivative of hexaethylene glycol, resulting in the overall formation of catenate **40** [87].

Howard and Ward's 4′-(3,4-dihydroxy)-2,2′:6′,2″-terpyridine (**13i**) is capable of coordination to a second metal centre through the potentially bidentate catechol donor set [32]. Similarly, 4′-(4-pyridyl)-2,2′:6′,2″-terpyridine (**14b**) has a pyridine ring remote from the 2,2′:6′,2″-terpyridine donor set which can be protonated or methylated to give a quaternary nitrogen centre [98].

5. Synthesis of multinucleating 2,2′:6′,2″-terpyridine ligands

The 'back-to-back' 2,2′:6′,2″-terpyridine ligand 6′,6″-bis(2-pyridyl)-2,2′:4′,4″:2″,2‴-quaterpyridine (**41a**) can be prepared in good yield by the nickel(0) coupling of two molecules of 4′-chloro-2,2′:6′,2″-terpyridine (**19c**) [51,52]. This ligand may be also successfully generated in situ in a binuclear complex by the nickel(0) coupling of



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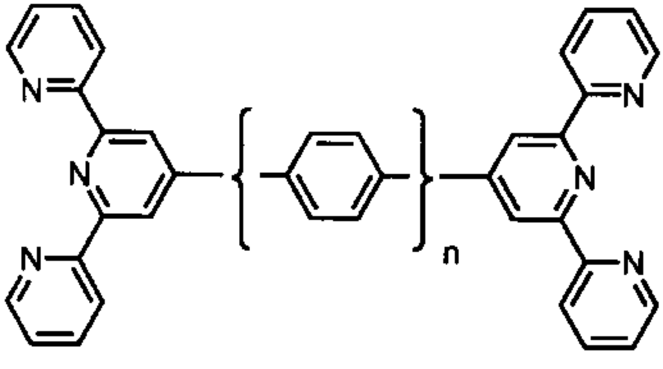
two equivalents of the corresponding mononuclear complex containing coordinated **19c** [144]. The bis-phenylene-bridged 'back-to-back' terpyridine ligand 4,4′-bis{4′-(2,2′:6′,2″-terpyridinyl)}biphenyl (**41c**) can similarly be prepared by the nickel(0) coupling of two equivalents of 4′-(4-chlorophenyl)-2,2′:6′,2″-terpyridine (**13b**) [55] or of 4′-(4-bromophenyl)-2,2′:6′,2″-terpyridine (**13c**) [53].



41a n = 0

41b n = 1

41c n = 2

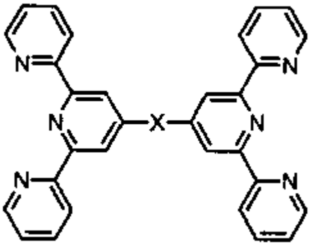
The 'back-to-back' 2,2′:6′,2″-terpyridine ligand, 1,4-bis{4′-(2,2′:6′,2″-terpyridinyl)}-benzene (**41b**), which incorporates a *para*-phenylene spacer functionality, can be prepared in two steps by a Kröhnke strategy [4]. The reaction of two equivalents of 2-acetylpyridine with one equivalent of benzene-1,4-dicarboxaldehyde (terephthalaldehyde) in basic ethanol yields a bis-enone, 1,4-bis{3-(2-pyridyl)-3-oxopropenyl}benzene. This is then condensed with two equivalents of the ylid precursor *N*-{1-(2′-pyridyl)-1-oxo-2-ethyl}pyridinium iodide (**6**) and excess ammonium acetate to give the binucleating ligand in 42% yield. Alternatively, a tetraketone species can be prepared by the reaction of benzene-1,4-dicarboxaldehyde with 4.5 equivalents of 2-acetylpyridine in basic aqueous ethanol at ambient temperature. Ring closure is then performed using ammonium acetate in ethanol at reflux [52]. Constable et al. have reported the crystallographically characterized 1,1′-bis(2,2′:6′,2″-terpyridin-4′-yl)ferrocene (**42a**) prepared from ferrocene-1,1′-dicarboxaldehyde by the Kröhnke methodology [26].

The same Kröhnke-type methodology may be employed to synthesize the potentially trinucleating ligand 1,3,5-tris{4′-(2,2′:6′,2″-terpyridinyl)}benzene (**43**) via a tris-enone from 1,3,5-benzenetricarboxaldehyde [52,145]. The reaction of the trialdehyde with 2-acetylpyridine does not proceed past the tris-enone to give a hexa-ketone, presumably for steric reasons.

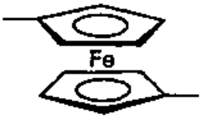
The 'back-to-back' ligand **42b**, incorporating a phenyl-bicyclo[2.2.2]octane-phenyl spacer has been prepared by Collin and co-workers by the palladium(0)-catalysed Suzuki cross-coupling of a boronate diester of the bridging unit with two equivalents of 4′-bromo-2,2′:6′,2″-terpyridine [56]. Grosshenny and Ziessel have prepared mono-ethynyl-bridged 'back-to-back' ligands **42c** and **42d** by the palladium(0)-catalysed Heck cross-coupling of stoichiometric amounts of the corresponding bromo-substituted (**19f**, **13c**) and ethynyl-substituted (**19g**, **13v**) 2,2′:6′,2″-terpyridines. The butadiynyl-bridged analogues **42e** and **42f** are obtained by the dimerization of the ethynyl-2,2′:6′,2″-terpyridine monomers **19g** and **13v** respectively, in the presence of CuCl and $CuCl_2$ [54]. Three 'back-to-back' 4′-ethynyl-2,2′:6′,2″-terpyridine ligands incorporating 5,5′-substituted-2,2′-bipyridyl (**42g**), 6,6′-substituted-2,2′-bipyridyl (**42h**) and 2,9-substituted-1,10-phenanthryl (**42i**) spacers have also been prepared [146].

4′-Hydroxy-2,2′:6′,2″-terpyridine (**19a**) can be coupled with 4′-chloro-2,2′:6′,2″-terpyridine (**19c**) using potassium hydroxide in *N*,*N*-dimethylformamide at reflux to give the oxygen-bridged 'back-to-back' ligand bis(2,2′:6′,2″-terpyridin-4′-yl)ether (**42j**) in good yield. Furthermore, as observed in the synthesis of 4′-(*N*,*N*-dimethylamino)-2,2′:6′,2″-terpyridine (**19e**), coordination of the 4′-chloro-2,2′:6′,2″-terpyridine to a metal centre activates it towards attack by the nucleophilic deprotonated 4′-hydroxy-2,2′:6′,2″-terpyridine. The dinucleating ligand **42j** differs from the other dinucleating ligands in that the oxygen spacer imposes an approximately tetrahedral angle between the terpyridine functionalities, as has been determined crystallographically [57]. Newkome and co-workers have used a similar coupling strategy to assemble an arborol ligand incorporating twelve 2,2′:6′,2″-terpyridine functionalities, and have incorporated this in a dodecanuclear metallomicellanol (Fig. 1) [115].

Sauvage and co-workers have prepared binucleating ligand **42k** containing two 2,2′:6′,2″-terpyridine functionalities linked by a porphyrin spacer unit. The ligand is

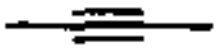


X =

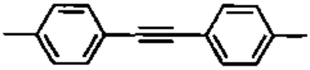


42a

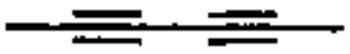
42b



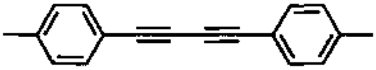
42c



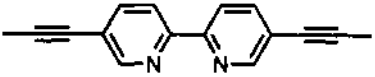
42d



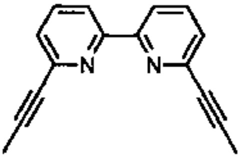
42e



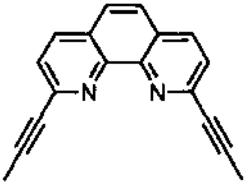
42f



42g

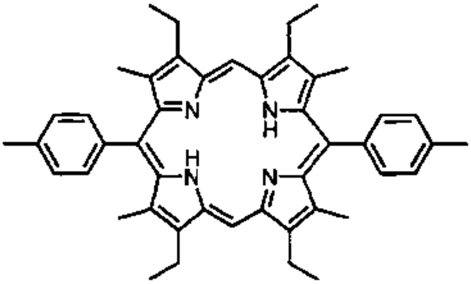


42h

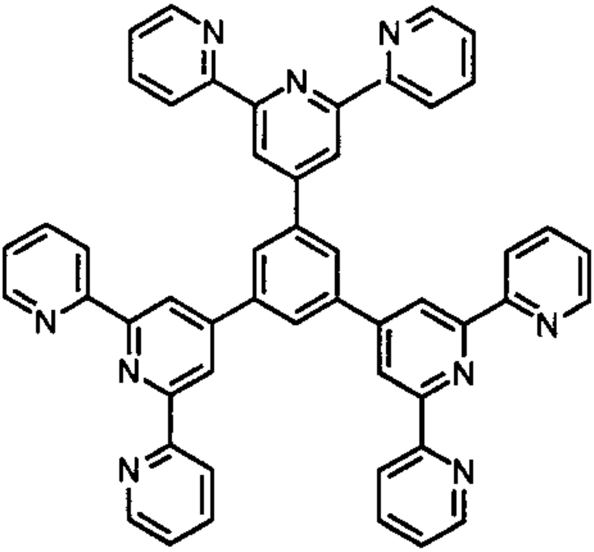


42i

42j



42k



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obtained by assembling the porphyrin ring by the 2:2 reaction of equimolar quantities of 4-{4′-(2,2′:6′,2″-terpyridinyl)}benzaldehyde (**13u**) and a dipyrrylmethane [29,31].

The reaction of 6-methyl-2,2′:6′,2″-terpyridine (**21b**) with lithium diisopropylamide results in deprotonation of the methyl group to give a carbanion. Taylor et al. have reacted this species with symmetrical diketones, such as 1,4-cyclohexanedione, to give the corresponding bridged bis(2,2′:6′,2″-terpyridin-6-yl) ligands of which **44** is typical. The bis-osmium complexes of these ligands have been investigated for potential curariform activity [125]. The same strategy has been used to prepare the helicating bis-terpyridine ligand **45** from 6-(4-methoxyphenyl)-5″-methyl-2,2′:6′,2″-terpyridine [147].

The ligands **46a** and **46b** consist of a 2,2′:6′,2″-terpyridine functionality linked 'back-to-back' with a 6-phenyl-2,2′-bipyridine donor set, a potentially cyclometallating analogue of 2,2′:6′,2″-terpyridine. These ligands are prepared from the corresponding 2,2′:6′,2″-terpyridine-carboxaldehydes (**19s** and **13u**) via a Kröhnke-type strategy [148,149].

6. Annelated derivatives of 2,2′:6′,2″-terpyridine

Over the last 10 years, interest has grown in annelated derivatives of 2,2′:6′,2″-terpyridine, that is to say terpyridine ligands with additional saturated or unsaturated 3,3′- and 5′,3″-linkages. Conformational constraints imposed upon these ligands by the additional linkages may be used to confer subtle changes to the properties of

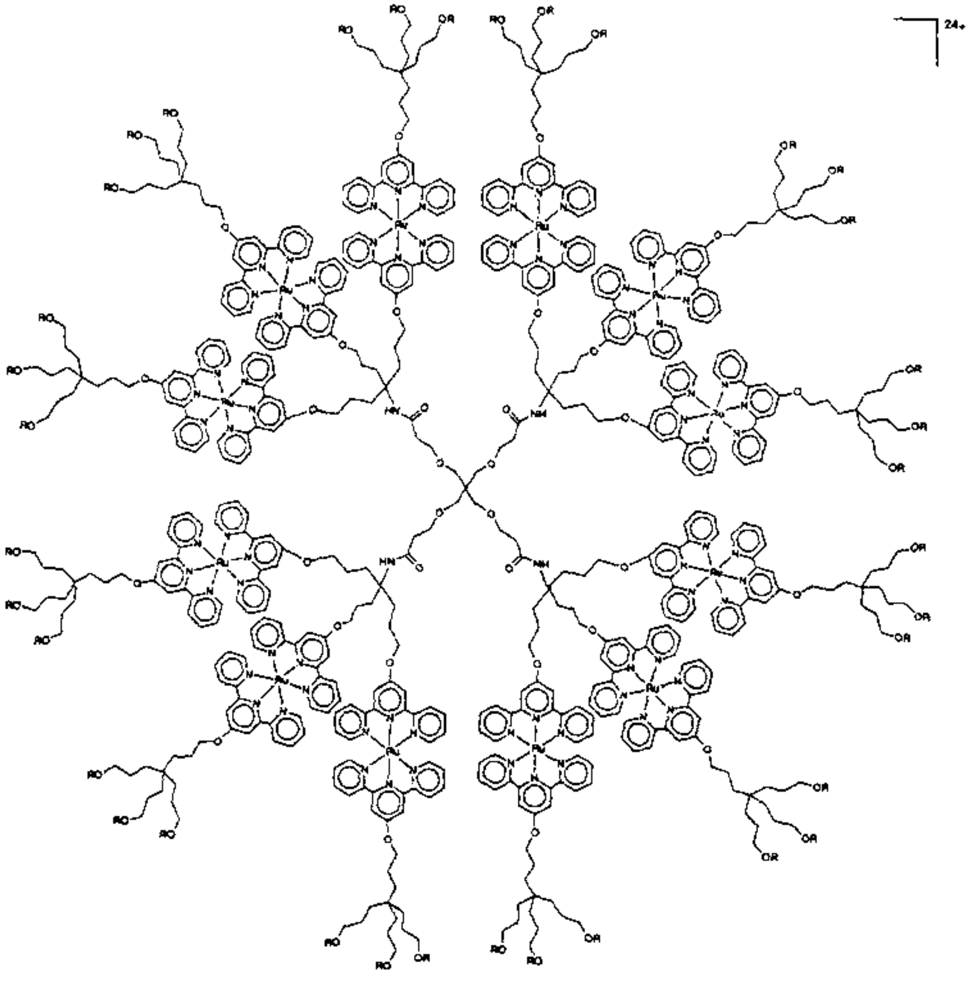
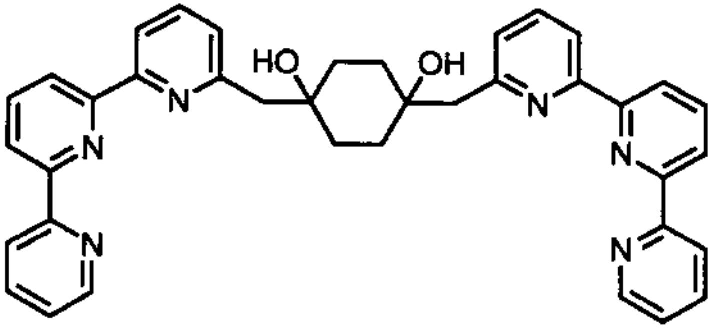


Fig. 1. Newkome and Constable's dodecanuclear metallomicellanol, $R = CH_2C_6H_5$ (reproduced with permission [115]).

the resulting coordination complexes. Koft and Case first prepared planar quino-[8,7-*b*][1,10]-phenanthroline (**47**) by performing the double Skraup reaction of glycerol, concentrated sulphuric acid and 3-nitrobenzenesulphonic acid with 4,5-diaminoacridine [150]. In this tridentate analogue of 1,10-phenanthroline the three nitrogen atoms are *preorganized* for coordination to a metal centre. This contrasts with free 2,2′:6′,2″-terpyridine for which adjacent pyridine rings adopt a conformation such that the nitrogen atoms are trans to each other, as is discussed in Section 7).

Thummel and Jahng have prepared annelated 2,2′:6′,2″-terpyridine derivatives **48b**, **48c**, and **48d** with saturated bis-, tris- and tetra-methylene bridges respectively, though the yields are somewhat disappointing. Their 2,6-di(2′-quinolyl)pyridine



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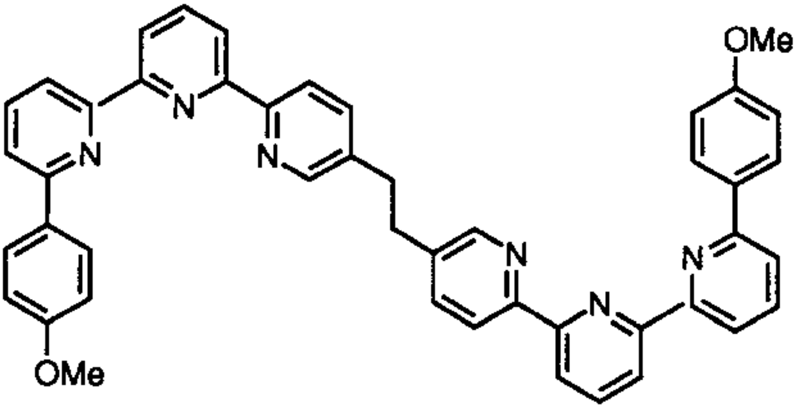

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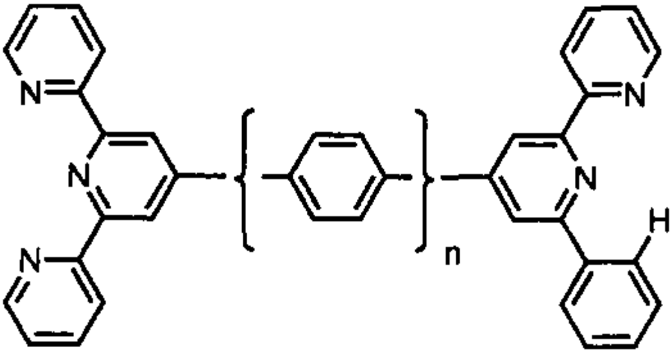
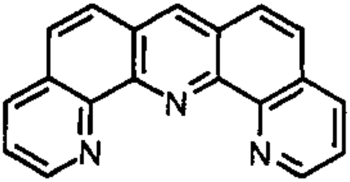
(**49a–c**) and 2,6-di(1′,8′-naphthyrid-2′-yl)pyridine (**50a–c**) analogues have been obtained in much higher yield by the same method, which is based on Friedlander condensations. Analysis by ^{1}H NMR indicated that the ligands containing tetramethylene bridges which are conformationally rigid at room temperature and exist as diastereomeric *meso* and *d,l* forms [151]. More recently, the same group have developed an alternative route to ligands containing two bis-methylene bridges based on a standard terpyridine synthesis. Condensation of the morpholine enamine of 6,7-dihydro-5*H*-quinolinone with an aldehyde, followed by Michael addition of a second enamine, affords a 1,5-diketone intermediate. Annelated **48b** may be prepared from paraformaldehyde in this way in a more acceptable yield of 31%, while use of the appropriate aryl aldehydes affords aryl substituted **51a–j** in 19–53% yields. The annelated 'back-to-back' ligand **52** may be prepared from terephthalaldehyde [99]. Risch and co-workers have discussed the problem of applying this enamine route to aliphatic aldehydes which are readily enolized, so facilitating side reactions [152].



46a n = 0
46b n = 1



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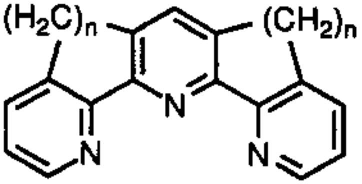
Using a novel, efficient one-step method, ligands **48a** (42%) and **48b** (48%) were prepared by reacting dimethylmethyleneammonium chloride with 5,6-dihydro-7*H*-1-pyrindin-7-one and 6,7-dihydro-8(5*H*)-chinolinone respectively [153].

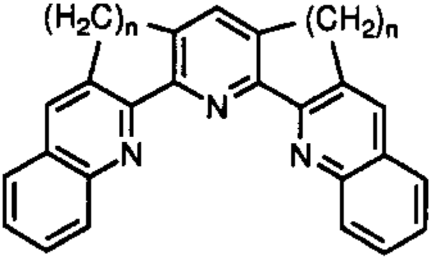
Anslyn and co-workers took advantage of the twist imposed on the terpyridine moiety by unsaturated 3,3′- and 5′,3″-linkages to design polyaza cleft molecules **53a** and **53b** capable of complexing cyclohexane polyols [154,155]. Bell and co-workers have prepared **54**, which is rendered soluble by two *n*-butyl side chains [156]. Symmetric bis-functionalization of **54** has permitted the synthesis of a hexadentate rigid toroidal macrocycle, or torand [157], while monofunctionalization has provided a route to pentadentate and heptadentate ligands with a helical twist [158].

7. Conformation of 2,2′:6′,2″-terpyridine ligands

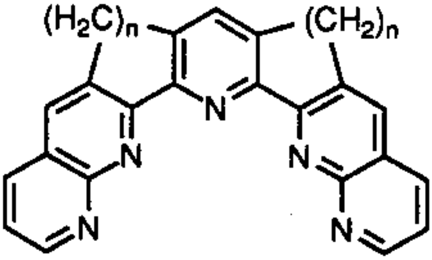
As free ligands, the oligopyridines are expected to adopt a planar conformation with the nitrogen atoms in adjacent rings trans to each other, so as to minimize the repulsion between the nitrogen atom lone pairs and also to minimize the molecular



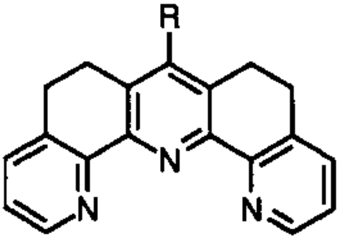
48a n = 1
48b n = 2
48c n = 3
48d n = 4



49a n = 2
49b n = 3
49c n = 4

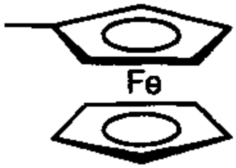


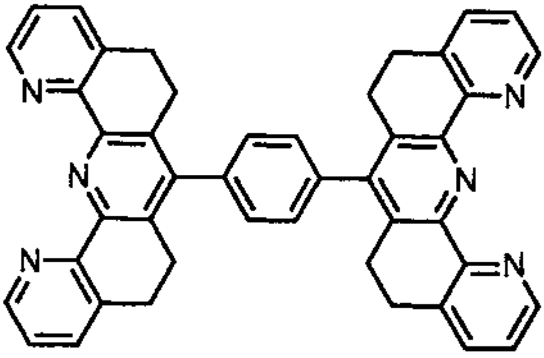
50a n = 2
50b n = 3
50c n = 4



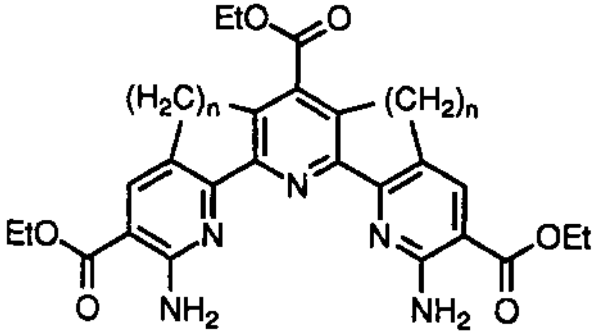
51a R = C_6H_5
51b R = C_6H_4Me-4
51c R = C_6H_4Cl-4
51d R = $C_6H_4NO_2$-4
51e R = $C_6H_4OCH_2C_6H_5$
51f R = $C_6H_4NMe_2$-4
51g R = $C_6H_3(OMe)_2$-2,5
51h R = 3-pyridyl
51i R = 4-pyridyl

51j R =

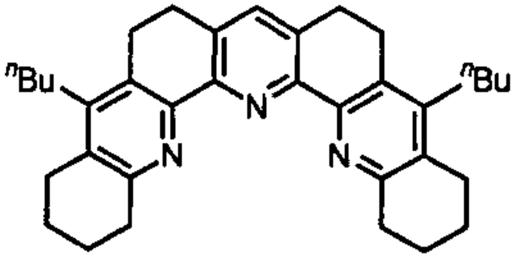




52



53a n = 2
53b n = 3



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dipole moment [85]. Planarity is preferred as this will maximize delocalization in the species. The adoption of the trans conformation in the solid state has been confirmed crystallographically for 2,2′:6′,2″-terpyridine [159], 4′-phenyl-2,2′:6′,2″-terpyridine (**2**) [77], 4′-(4-methylphenyl)-2,2′:6′,2″-terpyridine (**13e**) [160], 4′-(4-pyridyl)-2,2′:6′,2″-terpyridine (**14b**) [160], 4′-ferrocenyl-2,2′:6′,2″-terpyridine (**16a**) [24,25], 4′-methylsulphonyl-2,2′:6′,2″-terpyridine (**19b**) [160], 4′-(*N*,*N*-dimethylamino)-2,2′:6′,2″-terpyridine (**19e**) [19] and 6,6″-dibromo-4′-phenyl-2,2′:6′,2″-terpyridine (**30b**) [161]. All of the heterocyclic rings are approximately coplanar in each case. The four 'back-to-back' bis-terpyridine ligands 6′,6″-bis-(2-pyridyl)-2,2′:4′,4″:2″,2‴-quaterpyridine (**41a**) [162,163], 4,4′-bis{4′-(2,2′:6′,2″-terpyridinyl)}biphenyl (**41c**) [55], 1,1′-bis(2,2′:6′,2″-terpyridin-4′-yl)ferrocene (**42a**) [26] and bis(2,2′:6′,2″-terpyridin-4′-yl)ether (**42j**) [57] have also been crystallographically characterized. In all cases, each 2,2′:6′,2″-terpyridyl functionality adopts an approximately planar trans conformation, though in **41a** the terminal pyridine rings are rotated ca. 23° about the interannular bonds with respect to the central pyridine rings. Despite this, the two terpyridyl functionalities are effectively coplanar, whereas in **41c**, they are mutually perpendicular to each other, with the phenylene units at 26.3° to the adjacent terpyridine functionality.

For a free terpyridine to coordinate to a metal centre in a tridentate fashion, it must adopt the cis–cis conformation. The attachment process probably occurs by the coordination of successive pyridine rings to the metal.

8. Conclusion

Since Morgan and Burstall first isolated 2,2′:6′,2″-terpyridine in low yield from the mixture of oligopyridines obtained by the oxidative coupling of pyridine by iron(III) chloride over 60 years ago [1], the varied and exciting coordination chemistry of 2,2′:6′,2″-terpyridine [3] has led to the development of synthetic strategies enabling it and a wide range of its substituted analogues to be prepared in good yield on gram or multigram scales. An important recent development has been the design of multinucleating ligands incorporating two or more remote 2,2′:6′,2″-terpyridine metal-binding domains, permitting the extension of this area of coordination chemistry from the molecular to the supramolecular level [49,50,59,60].

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