Chiral 2,2′-bipyridines: ligands for asymmetric induction

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1 Introduction

2,2′-Bipyridine and its derivatives have received unprecedented attention due to their remarkable chemistry, both as compounds in their own right and because of their exceptional coordination chemistry.[1,2] Unlike many other common ligand systems such as cyclopentadienyls and phosphines, they are extremely stable in both aqueous solution and to atmospheric oxygen simplifying both their preparation and long-term storage. In addition, the possibility to include further functionality at any of the eight carbon atoms in the two pyridine rings has been extensively explored.[3,4]

Over the last thirty years 2,2′-bipyridine complexes of virtually every metal in the periodic table have been described.[1,2] This chelating ligand presents two nitrogen atoms to the metal centre in an almost ideal configuration, with only the rotation in the pyridyl–pyridyl bond being restricted upon complex formation. This results in extremely stable species, even with the more labile metal ions. The two excellent primary σ-dative interactions are further enhanced by the opportunities for overlap between the aromatic π-system and the d orbitals of coordinated transition metal ions.

This unique family of ligands also possesses accessible redox chemistry as a consequence of the π-conjugation, both as quaternary ammonium salts[5] and as ligands in coordination complexes. One area of extensive research that has developed as a consequence of this has been their use in photo-activated species; by coordination to an appropriate transition metal such as ruthenium(II), osmium(II) or rhenium(I).[3,6–8] In such complexes an electron can be excited from the metal to the ligand (metal to ligand charge transfer). In order to fine tune such systems to a particular purpose, a large range of substituted 2,2′-bipyridine ligands have been described giving rise to exciting developments in such areas as photocatalysis[7] and luminescent molecular sensors.[9,10]

As in common with many bidentate ligands 2,2′-bipyridine imposes a helicity upon a coordinated metal centre in many common geometries.[11] Compared to the large volume of literature dedicated to the chirality at carbon centres though, metal centred stereochemistry has received little attention. Over the last decade, this issue of "inorganic" stereochemistry has become a major research topic driven by the potential application in such diverse fields of research as nanoscale technology, materials chemistry and asymmetric catalysis.[12] The coordination geometry of a transition metal centre is pivotal to both the reactivity and behaviour. As recently as 1999, von Zelewsky emphasized the issue saying *"The possibility to predetermine the chirality at metal centres is a relatively new field of basic research where new and unexpected results can be obtained"*.[12]

By far the most frequent method of controlling the stereochemistry of a metal centre is by using chiral ligands of known configuration. These transfer the chiral information stored in the ligand's structure to the metal centre. For this purpose a wide and varied number of species have been studied ranging from simple amino acids to far more complex multidentate systems.[12] As a general observation, the predetermination of chirality at the metal centre is not particularly efficient with monodentate ligands, whereas those with higher denticity often give rise to complete chiral induction. Advances in the non-racemic chiral functionalization of 2,2′-bipyridine over the last decade have opened new and exciting opportunities to influence both the metal centred stereochemistry and the chirality of other species coordinated to the same metal centre. Consequently, the familiar 2,2′-bipyridine structure is finding new applications in such areas as enantiomerically pure supramolecular lattices and homogeneous asymmetric catalysis.

The primary objectives of this article are to illustrate the variety of synthetic strategies that have been employed in the preparation of non-racemic chiral 2,2′-bipyridines, highlight their potential applications in structural control and to explore the recent developments in their use as asymmetric catalysts. In order to limit the scope, only species possessing chirality independent of metal complexation are considered, thus 3-substituted-2,2′-bipyridines and 1,1′-biisoquinolines have not been included. It should be noted though that both of these species are poor ligands in general and there are few examples with appended chiral substituents. Attention is drawn to the fact that many of the synthetic ideas discussed are directly applicable in the preparation of achiral ligands and have also been applied to the structurally similar 1,10-phenanthroline and tridentate ligand 2,2′:6′,2″-terpyridine.

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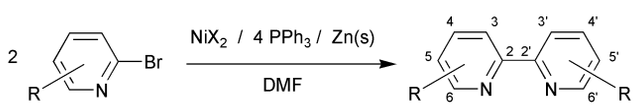
2 Synthetic strategies

The preparation of chiral 2,2′-bipyridines can be broken down into a number of alternative methodologies depending upon the target molecule. The synthesis of ligands possessing a C_2-axis of rotation has typically been achieved by coupling two halopyridines possessing the required chiral group. However, the synthetic routes to asymmetric (C_1) ligands have been attempted in a variety of ways. One common route mirrors that of the C_2 systems by coupling a second pyridine to the appropriately substituted halopyridine. Alternatively, the construction of the functionalized pyridyl ring using a cyclization of an unsaturated ketone possessing the required chirality (Kröhnke synthesis) has allowed the synthesis of some extremely intricate compounds. Somewhat surprisingly, the addition of chiral groups to a preprepared bipyridine possessing suitable substituents has not been explored until relatively recently.

2.1 C_2-Symmetric systems

2.1.1 Nickel(0) coupling reactions

The preparation of C_2-symmetric systems has generally been achieved by the coupling of two halopyridines bearing the appropriate substituents.[13–15] In a typical reaction, the vessel is charged with a nickel(II) halide and four to five equivalents of triphenylphosphine. The active nickel(0) species is then generated *in situ* by reduction with zinc powder. Following prolonged heating, the product is isolated in a yield anywhere between 35 to 90% (Scheme 1). As the examples highlighted below indicate,



Scheme 1 The standard coupling procedure for C_2-symmetric 2,2′-bipyridines (including the systematic numbering scheme for the carbon positions).

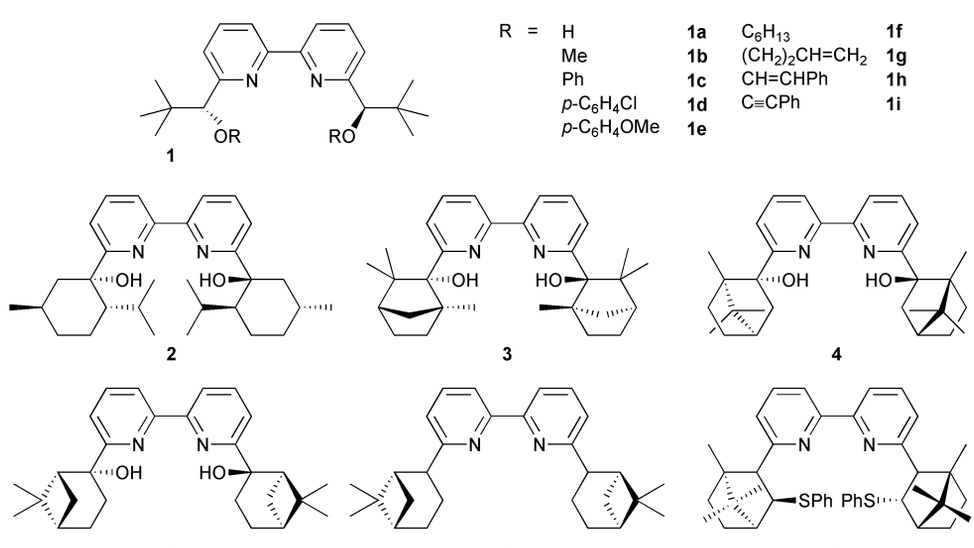
the coupling is particularly attractive since the chiral centres appended to the halopyridine retain their stereochemical integrity and reactive groups such as hydroxy and alkene moieties remain unaffected despite the apparently severe reaction conditions.

Bolm described one of the earliest examples of a non-racemic chiral 2,2′-bipyridine, namely molecule **1a** by coupling (*S*)-1-(6-bromopyridin-2-yl)-2,2′-dimethylpropanol, with the chirality having been introduced by the asymmetric reduction of the pyridyl ketone using (+)-isopinocampheylborane.[16,17] As in most of the species considered in this report, the introduced stereochemistry was retained upon coupling using a stoichiometric quantity of nickel(0). With the 2,2′-bipyridine possessing a free alcohol, etherification has been subsequently used to introduce a large number of alternative substituents **1b–i** (Scheme 2).[16–20]

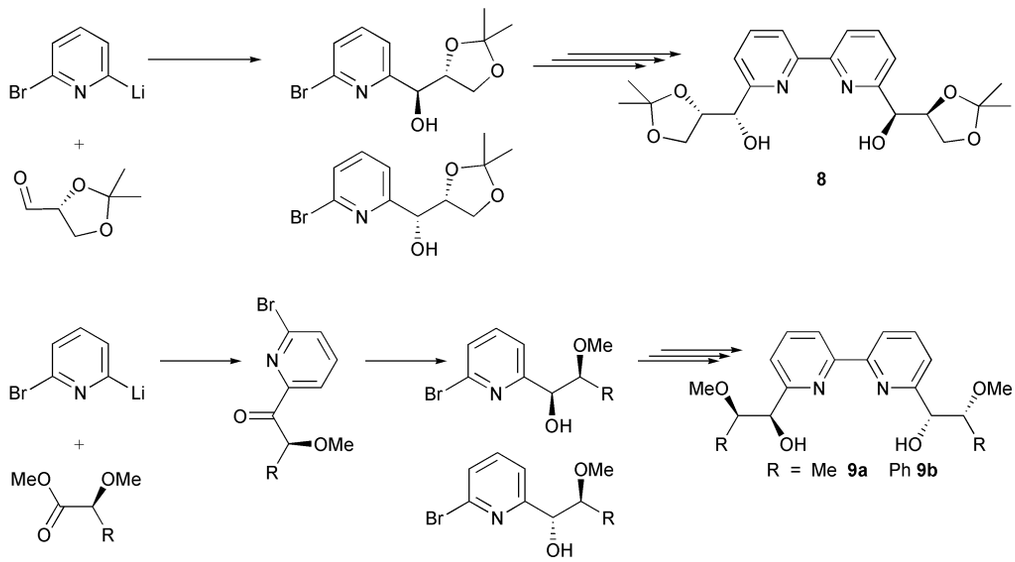
A similar strategy to that described by Bolm *et al.* has recently been employed in the introduction of chiral alcohol groups adjacent to the 6- and 6′-carbons of 2,2′-bipyridine. Kwong and co-workers have relied upon non-racemic chiral substituents arising from natural products ("chiral pool"), rather than upon complex asymmetric synthetic procedures. This approach to introduce enantiopure substituents has been widely investigated giving rise to a number of the molecules described subsequently. By reacting 2-bromo-6-pyridyllithium with the chiral aldehydes (−)-menthone, (*R*)-(−)-fenchone, (*R*)-(−)-camphor and (*R*)-(+)-nopinone, functionalized pyridines were prepared which were coupled under the standard conditions giving ligands **2–5** respectively.[21,22] These diols can be dehydrated to the alkene creating possibilities to change functional groups. Subsequent reduction, starting from **5**, leads to the bis-pinenyl ligand **6** which has been used in asymmetric catalytic procedures by Chelucci.[23] The alkene arising from the dehydration of **4** has allowed the synthesis of the thioether **7**.[24]

Moberg and co-workers demonstrated the difficulty of preparing 2,2′-bipyridines possessing chiral alcohols **8** and **9** (Scheme 3).[25] Unlike the previous examples, the reaction of 2-bromo-6-pyridyllithium with (*R*)-2,3-*O*-isopropylideneglyceraldehyde (prepared from D-(+)-mannitol) led to a diastereoisomeric mixture of products which required chromatographic separation. The coupling procedure again was performed under the typical conditions to give diol **8**, although in this case the alcohols were protected as the *tert*-butyldimethylsilyl ether (TBDMS) for the reaction in a disappointing 54% yield (Scheme 3).[25] In the same article, the structurally similar diols **9a** and **b** are reported by the reaction of 2-bromo-6-pyridyllithium with alkyl (*S*)-2-methoxypropionoate and L-mandelic acid giving rise to pyridyl ketones possessing a single chiral centre. Upon reduction, a diastereomeric mixture of alcohols was obtained which were separated by HPLC chromatography and coupled in a similar manner to ligand **8** giving **9a** and **b** respectively (Scheme 3).[25]

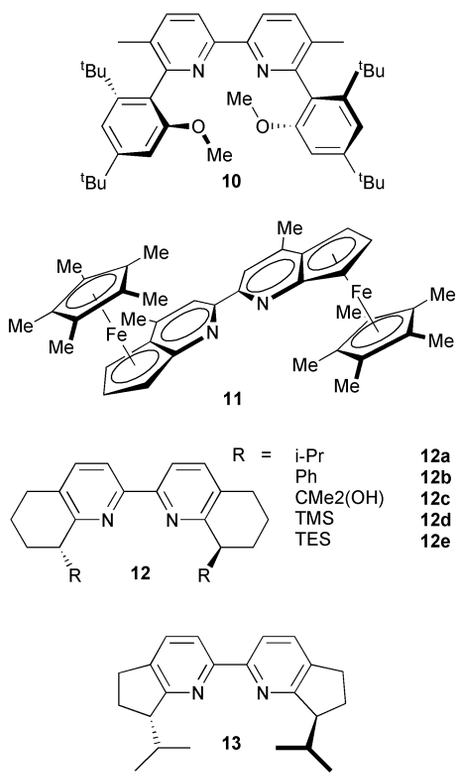
A different approach to the inclusion of chirality has been adopted by Wong *et al.* by exploiting the use of atropisomerism. Following their success in the chiral resolution of sterically hindered pyridyl-phenols, the nickel(0) activated coupling gave bipyridine **10** (Scheme 4).[26] The use of planar chirality has also



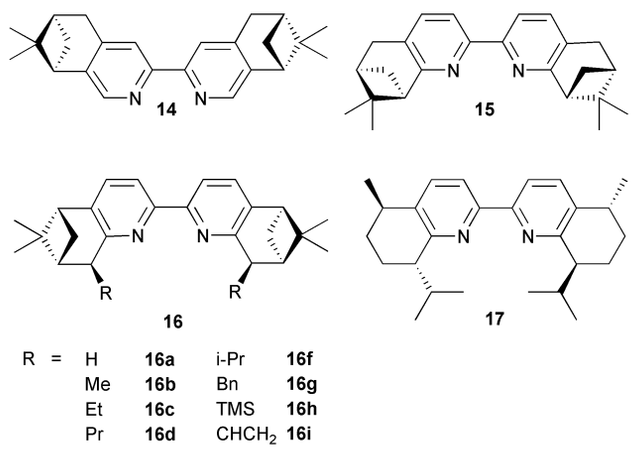
Scheme 2 C_2-symmetric 2,2′-bipyridines possessing non-racemic diol groups **1–5** and their derivatives **6** and **7**.



Scheme 3 The synthetic route to the C_2-symmetric 2,2′-bipyridines possessing non-racemic diols **8** and **9**.[7]



Scheme 4 C_2-Symmetric 2,2′-bipyridines **10**–**13**.



Scheme 5 C_2-symmetric 2,2′-bipyridines **14**–**17** with the chirality derived from fused natural products.

been demonstrated with an η^5-organometallic fragment in a recent publication by Fu and co-workers. The coupling of a ferrocene derivative possessing a fused chloropyridine function, yet again upon a nickel(0) phosphine complex, gave only the racemic diastereoisomer in reasonable yield. The two enantiomers were subsequently separated using chiral HPLC techniques giving the unusual organometallic ligand **11**.[27] Both molecules **10** and **11** have shown remarkable activity as catalysts in asymmetric cyclopropanation reactions.

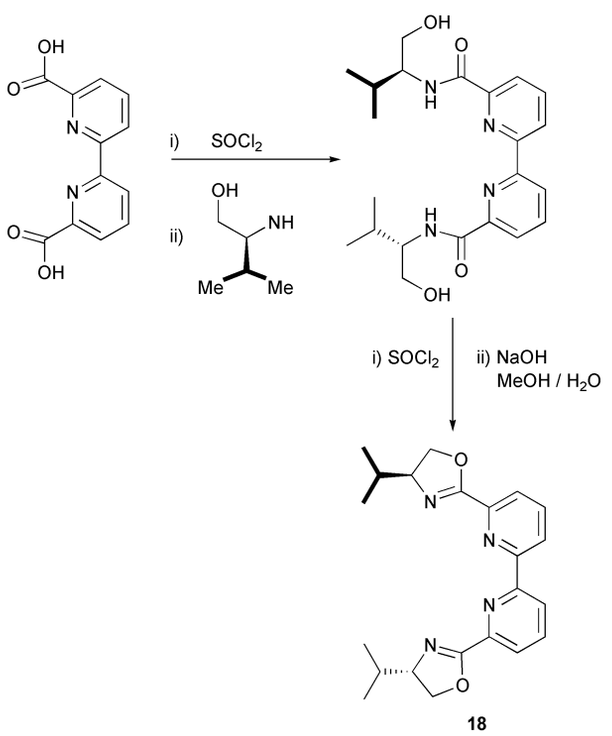
The inclusion of fused rings adjacent to the pyridine moiety such as those used in the preparation of the bis-ferrocene complex **11** has been a recurrent theme (Scheme 4 and 5) as it introduces rigidity into the ligand framework. Katsuki *et al.* illustrated a number of years ago that the lithiation of 2-chloro-5,6,7,8-tetrahydroquinoline followed by the introduction of an appropriate halide led to a chiral centre adjacent to the 6-position of the pyridine ring. The racemic mixture was separated using HPLC, and coupled upon nickel(0) giving rise to the bipyridine **12**. Likewise, the analogous cyclopentene gave ligand **13**. Further studies led to the discovery that the chirality could also be introduced by stereoselective epoxidation and alkylation, giving the product with an enantiomeric excess (ee) of 96% thus avoiding the time-consuming and expensive chromatographic procedure.[28–30]

Fused pyridyl ring systems, derived from chiral ketones taken from the "chiral pool", have been demonstrated by a number of research groups. In particular, the group of von Zelewsky has developed a range of pinenyl functionalized 2,2′-bipyridine systems. The C_2-symmetric difunctionalized (4,5),(4′,5′)-dipinenyl-2,2′-bipyridine **14**, derived from (*R*)-(−)-myrtenal was initially prepared *via* a two stage Kröhnke synthesis similar to that used in the preparation of the asymmetric molecule **38** discussed below.[31,32] However, two simpler methods relying on a single Kröhnke reaction to the appropriate halogenated pyridine and the standard nickel(0) coupling gave rise to the ligand **14** in just three steps.[33–35] In addition to the 4,5-fused system, similar terpenoid functionality has been introduced at the 5,6-carbon positions using an almost identical synthetic procedure giving the bis-pinenyls **15** from (+)-nopinone and **16** from (+)-pinocarvone.[32,34–38] The latter readily undergoes a stereospecific lithiation at the pinenyl methylene carbon adjacent to the pyridine ring, allowing a large range of substituents to be appended.[34,36–38] While pinene derivatives remain the most studied chiral appendage, the enantiomeric pair of the

menthone derived species **17** have also recently been reported by Kocovsky and co-workers.[34]

2.1.2 C_2-Symmetric systems prepared by secondary functionalization

The introduction of non-racemic chirality to the preprepared 2,2′-bipyridine framework has not been widely explored. This in part is as a consequence of the remarkable efficiency of the nickel(0) coupling reactions widely used in the synthesis of the C_2-systems. However, it is also important to realise that the introduction of enantiopure groups is reliant upon the availability of suitable substituents on the 2,2′-bipyridine by which to attach them. These precursors typically require a multi-step synthetic procedure in their preparation, giving the target materials in low yield. One of the most accessible groups of building blocks are the dicarboxy-2,2′-bipyridines prepared by the oxidation of the appropriate dimethyl-2,2′-bipyridines.[39–41] There are examples of disubstitution at the (6,6′)-, (5,5′)- or (4,4′)- positions offering a range of possibilities to add chiral substituents (Scheme 1). (Note 3,3′-dicarboxy-2,2′-bipyridine is also available, usually prepared by the oxidation of 1,10-phenanthroline.[42]) As an example, 6,6′-dicarboxy-2,2′-bipyridine was used in the preparation of **18**, by conversion to the acyl chloride with thionyl chloride and subsequent reaction with (*S*)-(+)-2-amino-3-methylbutan-1-ol (L-valinol) (Scheme 6).[43]



Scheme 6 The synthetic route to the C_2-symmetric 2,2′-bipyridine **18** from 6,6′-dicarboxy-2,2′-bipyridine.

Following conversion of the free alcohol to the chloride and base induced cyclization, **18** was obtained in reasonable overall yield.

The same 6,6′-dicarboxy-2,2′-bipyridine precursor used in the preparation of **18** was used in the high dilution synthesis of a series of enantiopure chiral 2,2′-bipyridines macrocycles derived from simple diamino acids (prepared from either (*S*)-(+)-valine or (*S*)-(−)-proline) giving **19** and **20** (Scheme 7).[44,45] 5,5′-Dicarboxy-2,2′-bipyridine has also been employed by conversion to the acyl chloride and reaction with chiral amino acids to give the diamides **21a**–**d**.[46] Likewise there are several examples derived from 4,4′-dicarboxy-2,2′-bipyridine by amidification with amines bearing a chiral centre to yield the series of ligands **22a**–**e**.[47–49] Alternatively, esterification with (−)-menthol gave ligand **23**.[48,50] It should be noted that 4,4′-difunctionalized-2,2′-bipyridine systems (Scheme 1) have been extensively explored with regard to non-chiral systems because of the commercial availability of 4,4′-dimethyl-2,2′-bipyridine. There are however remarkably few chiral groups that have been appended at these positions. This can be accounted for by considering the diminished steric influence a chelated metal experiences from this position when compared to the 5 and 6-positions. And so the species such as **22** and **23** have been primarily used to influence chirality of other species in solution (Section 3.1.3).

As an alternative to the dicarboxy-2,2′-bipyridine precursor, chiral groups can be appended to the molecular scaffold *via* nucleophilic halide substitution. Telfer *et al.* have described the synthesis of the amino acid functionalized ligand **24**, from the precursor 5,5′-bis(chloromethyl)-2,2′-bipyridine.[51] Furthermore, Stechan and co-workers have described the preparation of two ligands bearing camphor sultam moieties by the copper catalysed aromatic nucleophilic substitution of 6,6′-dibromo-2,2′-bipyridine (**25a**) and the base induced coupling of 6,6′-bis(bromomethyl)-2,2′-bipyridine (**25b**).[52]

2.2 C_1-Symmetric systems

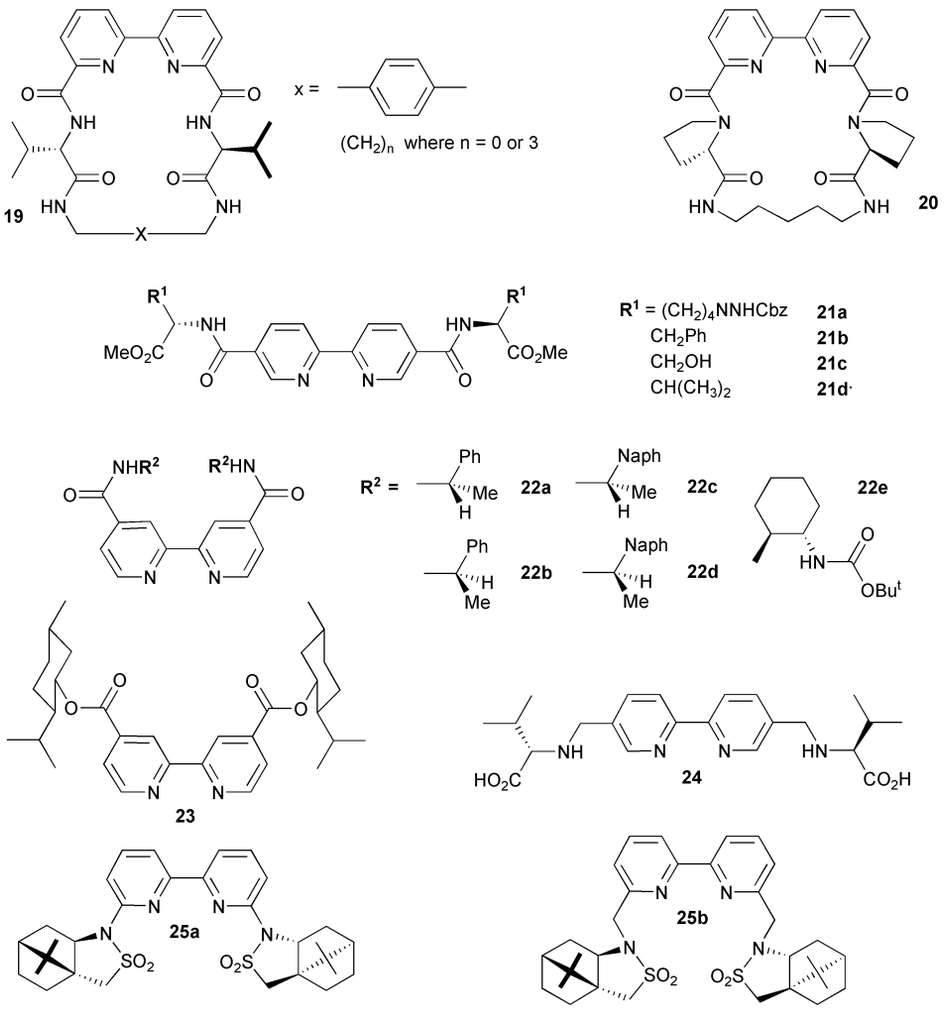
2.2.1 Coupling reactions

As a natural extension to the preparation of chiral C_2-symmetric systems *via* a nickel(0) coupling, Bolm successfully explored the possibility of using a cross coupling reaction to a second pyridyl, giving rise to a C_1-symmetric 2,2′-bipyridine analogous to compound **1**.[16–18,53] Combining either (2-pyridyl)-tributyltin(IV) in a "Stille type" or 2-pyridylzinc chloride coupling with the previously discussed 6-halopyridine (possessing the appropriate non-racemic chiral substituents) with a palladium(0) catalyst gave rise to ligand **26** in good yield (Scheme 8). Recently, Kwong has explored the same synthetic route to a range of asymmetric coupled bipyridines **27**–**29** (analogous to the C_2-symmetric systems **2**–**5**).[21,22] Somewhat surprisingly though, considering the number of halopyridines used in the synthesis of C_2 systems, there are only a limited number of examples obtained using this relatively simple synthetic approach.

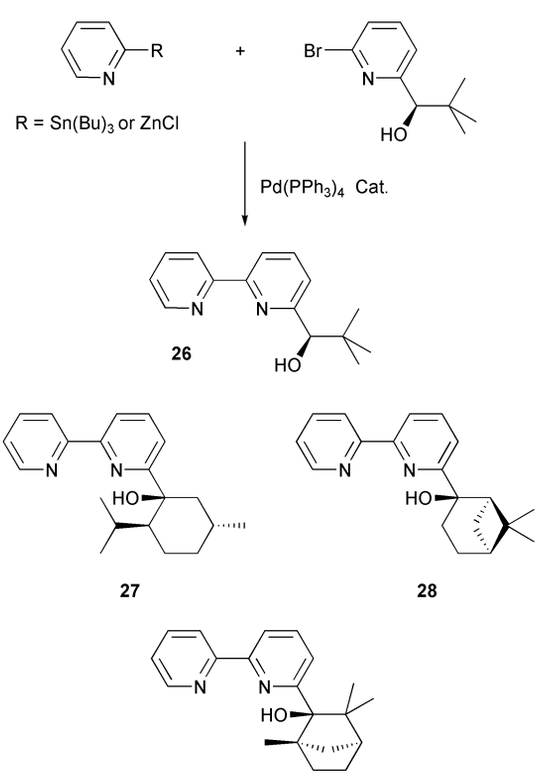
2.2.2 Co-cyclotrimerization reactions

Probably the most widely employed method in the synthesis of asymmetric 2,2′-bipyridine ligands is the formation of one of the pyridine moieties *via* a cyclization procedure. One of the earliest examples was described by Botteghi, namely the 6-substituted species **30**.[23,54–56] This simple system was derived, not from the appropriately substituted halopyridine, but from the analogous nitrile according to Scheme 9. The secondary unfunctionalized pyridine was created around the nitrile function by a co-cyclotrimerization with acetylene upon a cobalt(I) catalyst. In both the 6- and 4-substituted systems (**30** and **31** respectively) remarkably high yields (80%) were achieved. Unsurprisingly, this synthetic route has been limited to simple aliphatically substituted compounds due to the possibility of secondary reactions occurring to the appended chiral groups under the severe reaction conditions.

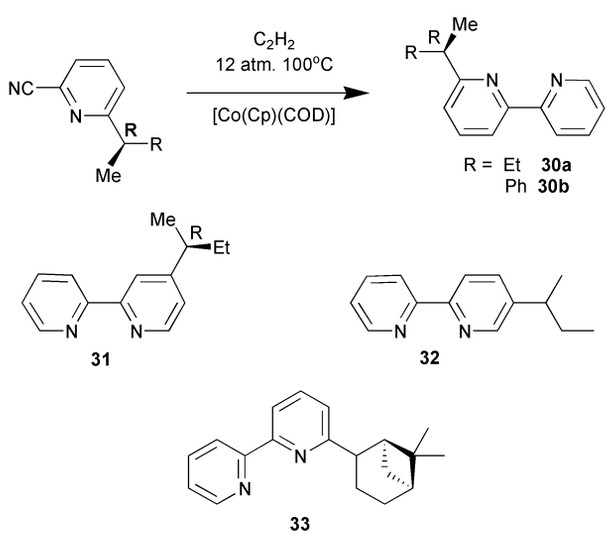
The preparation of the 4-substituted compound **31** was also achieved by the use of a multi-step procedure culminating in a condensation cyclization of a 1,5-diketone in the presence of hydroxylamine hydrochloride. This mechanism is very similar to that used in the subsequently described Kröhnke syntheses.[54,57] The 5-substituted compound **32**[57,58] and the structurally related compound **33** derived from naturally occurring (−)-*trans*-myrtanol have also been prepared by this method.[55] However, this cyclization gave **33** in only 20% and a better yield (85%) was obtained by the co-cyclotrimerization with acetylene of a cyanopyridine described above.[56]



Scheme 7 C_2-symmetric 2,2′-bipyridines **19**–**25** prepared by secondary functionalization of the 2,2′-bipyridine precursors.



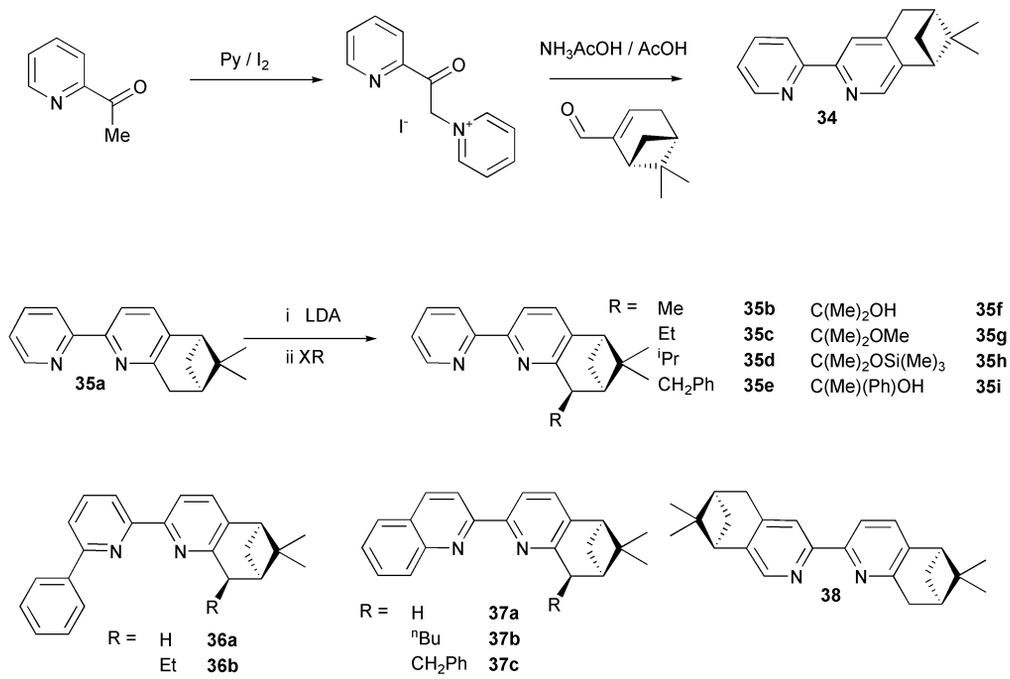
Scheme 8 The synthetic route to the C_1-symmetric 2,2′-bipyridines **26**–**29** *via* an asymmetric coupling procedure on a palladium catalyst.



Scheme 9 The synthetic route to the C_1-symmetric 2,2′-bipyridines **30**–**33** *via* a co-cyclotrimerization reaction of 2-cyanopyridine.

2.2.3 Kröhnke reactions

The versatile Kröhnke reaction has been the most common method used in the synthesis of C_1-symmetric polypyridyl ligand systems as it has allowed a considerable variety of substituents to be included at the 3,4,5 and 6 positions (including the preparation of fused rings).[59] The general procedure takes a pyridinium salt such as 2-acetylpyridine pyridinium iodide ("Kröhnke's Salt") with an α,β-unsaturated carbonyl.



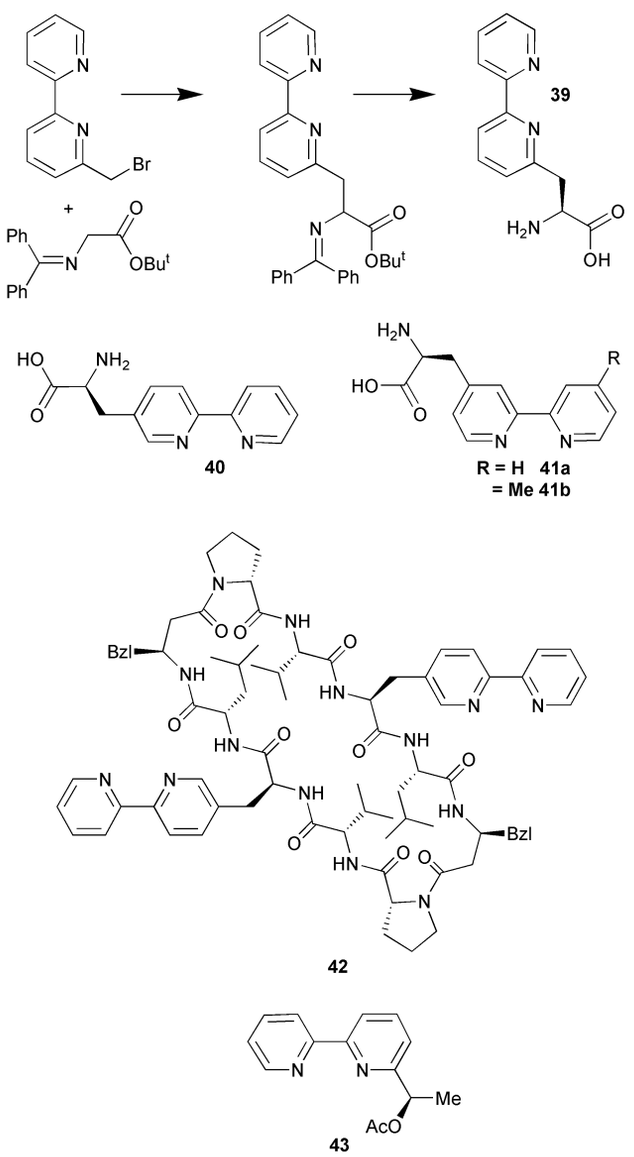
Scheme 10 The synthetic route to C_1-symmetric 2,2′-bipyridines **34**–**38** *via* a Kröhnke reaction.

The functionalized pyridine ring then forms by a double condensation with ammonia from ammonium acetate present in the reaction mixture (Scheme 10).

This approach was explored in the early 90's by the research group of von Zelewsky in the preparation of ligands **34** and **35a**.[60] By using "Kröhnke's salt" and commercially available (−)-myrtenal (**34**) and (+)-pinocarvone (prepared by oxidation of (−)-α-pinene) (**35a**), in the presence of ammonium acetate, yields of up to 80% have been achieved (Scheme 10).[60] In each case, as with the analogous difunctionalized bipyridines **14** and **16**, they readily undergo a stereospecific lithiation at the pinenyl methylene carbon adjacent to the pyridine ring facilitating the inclusion of further functionality. In the case of **34**, a single substituent can be appended[61] but this procedure has more commonly been used in the synthesis of a range of linked bipyridines which have been extensively reviewed elsewhere.[4,62] Ligand **35** on the other hand has been widely investigated in catalytic systems (discussed below). A variety of groups have been stereospecifically appended giving ligands **35b**–**i**.[34,37,63,64] By using a 2-acetylpyridine moiety bearing additional groups such as a phenyl ring in the formation of the Kröhnke salt, secondary groups can be introduced. For example, **36** was prepared from 2-acetyl-6-phenylpyridine[37] and **37** from 2-acetylquinoline.[65] Taking these ideas to extreme led to the initial synthesis of the C_2-symmetric systems **14** and **16** where both of the pinenyl substituted pyridine rings were prepared by cyclization in a stepwise double Kröhnke synthesis.[32,36,38] While a simpler route has been described,[33–35] this strategy gave rise to the possibility of preparing the asymmetric (4,5),(5′,6′)-dipinenyl-2,2′-bipyridine **38** using a nine step synthesis.[32]

2.2.4 C_1-Symmetric systems prepared by secondary functionalization

As with the C_2-symmetric species described above, the addition of a non-racemic chiral substituent to a suitable 2,2′-bipyridine precursor has not received as much attention as would be anticipated. However, this route has been studied for the preparation of amino acid functionalized systems by the reaction of 4, 5 or 6-bromomethyl-2,2′-bipyridine with *N*-(dimethylene)-glycine *tert*-butyl ester in the presence of the chiral phase-transfer catalyst (8*S*,9*R*)-*N*-benzylchinchidinium chloride giving **39**, **40** and **41a** (Scheme 11). The enantiomerically pure material is then isolated by crystallisation from the enriched



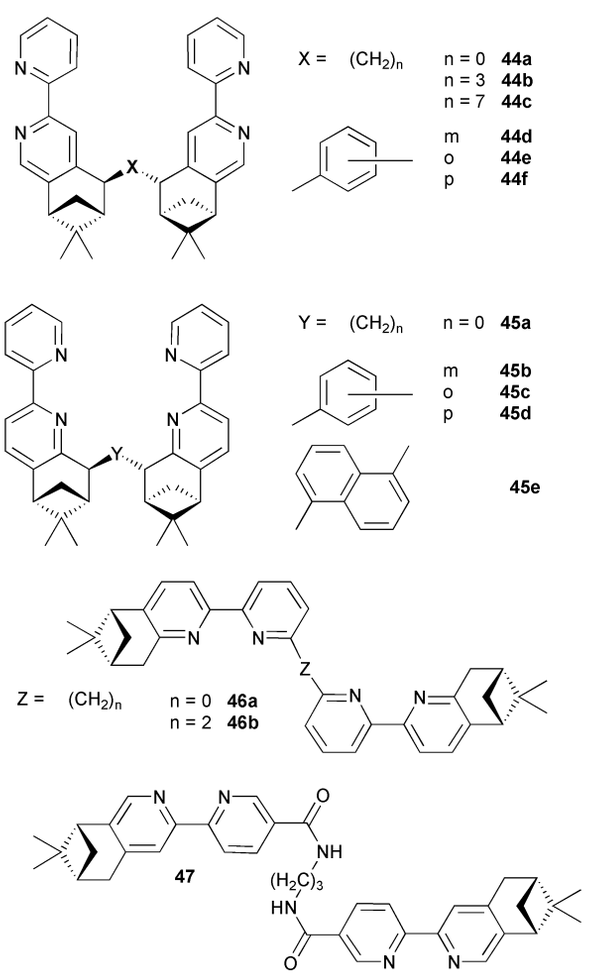
Scheme 11 C_1-symmetric 2,2′-bipyridines **39**–**43** prepared by secondary functionalization of 4-bromomethyl-4′-methyl-2,2′-bipyridine.

reaction product.[66–68] Bowler and co-workers have recently improved on the synthesis in the preparation of **41b**, by using alkaline protease in the isolation of the L (*S*)-enantiomer.[69] The availability of an amino acid with a bound 2,2′-bipyridine has opened new opportunities to the synthesis of artificial metalloproteins using such ligand systems as **42**.[70]

The addition of chiral substituents at the 6-position has also been demonstrated by the lithium mediated coupling of 6-bromo-2,2′-bipyridine with *N*,*N*-dimethylacetamide. Following reduction to the alcohol, the *R* and *S* isomers of **43** were isolated by lipase-catalyzed enantioselective acetylation.[71]

2.3 Systems containing more than one 2,2′-bipyridine

A large number of ligands containing two or more 2,2′-bipyridine units have been synthesized and have recently been the subject of a comprehensive review.[4] It is not the intention of this report to duplicate the work therein, but to draw attention to a number of examples where enantiopure chiral ligand systems have been synthesized and used in asymmetric induction (discussed below). The connection of two or more 2,2′-bipyridine groups possessing appended non-racemic chiral substituents has been dominated in the literature by von Zelewsky's "chiragen" (or *chiral gen*erator) series of ligands **44**–**47**. Using the pinenyl substituted 2,2′-bipyridine ligands **34**[33,60,72] and **35**,[73–75] the stereospecific lithiation at the pinenyl methylene carbon allows the introduction of a range of linkages between the two chelating groups, a selection of which are illustrated in Scheme 12. Furthermore, using similar synthetic procedures, **34** and **35**[76–79] have been connected *via* the pyridine ring not bearing the pinenyl function giving **46** and **47**. These have previously been included in a number of review articles and so will not be discussed in detail here.[4,62]



Scheme 12 The "chiragen" series of bridged 2,2′-bipyridines **44**–**47**.[22]

The introduction of a chiral linkage between two 2,2′-bipyridines moieties has generally been achieved by reaction of a suitable 2,2′-bipyridine precursor with the appropriate difunctionalised spacer. Lehn described an early example in collaboration with Bolm by using an analogue of **1** as the chiral linkage thus providing an additional bipyridine chelating group.[80] By reacting the chiral diol with sodium hydride in the presence of 6-bromomethyl-6′-methyl-2,2′-bipyridine, ligand **48** was obtained in 76% yield (Scheme 13). More recently, alternative chiral linkages have been inserted between two 2,2′-bipyridine groups using the same synthetic procedure. For example, Izatt and Bradshaw described the "podand" systems **49a** and **b**[81] and Cozzi and Siegel *et al.* demonstrate the use of an atropisomeric dialcohol in the preparation of the rigid molecule **50**.[82] Similarly, they illustrate the bridged species **51a**–**c** possessing linkages with a restricted rotation derived by the esterification of several bis-carboxylic acid spacers with 6-hydroxymethyl-6′-methyl-2,2′-bipyridine.[82,83] Along comparable lines Hodecova has recently described a series of species connected at the 3- and 3′-positions of binaphthol.[84] In order to achieve a range of linkages to the chiral spacer the paper describes the use of a number of 6-functionalised-bipyridines including 6-aminomethyl-2,2′-bipyridine and 6-amino-2,2′-bipyridine giving **52a** and **b** respectively. The linkage of 6-functionalised bipyridines with an enantiomerically pure spacer group has dominated the published examples. To address this we in Belfast are currently exploring the possibilities to introduce a chiral linkage at the 5-bipyridine position. The first example of which has recently been reported connecting 5-carboxy-2,2′-bipyridine with commercially available (*R*,*R*) and (*S*,*S*)-1,2-diaminocyclohexane giving rise to the diamide **53**.[85]

3 Possible applications

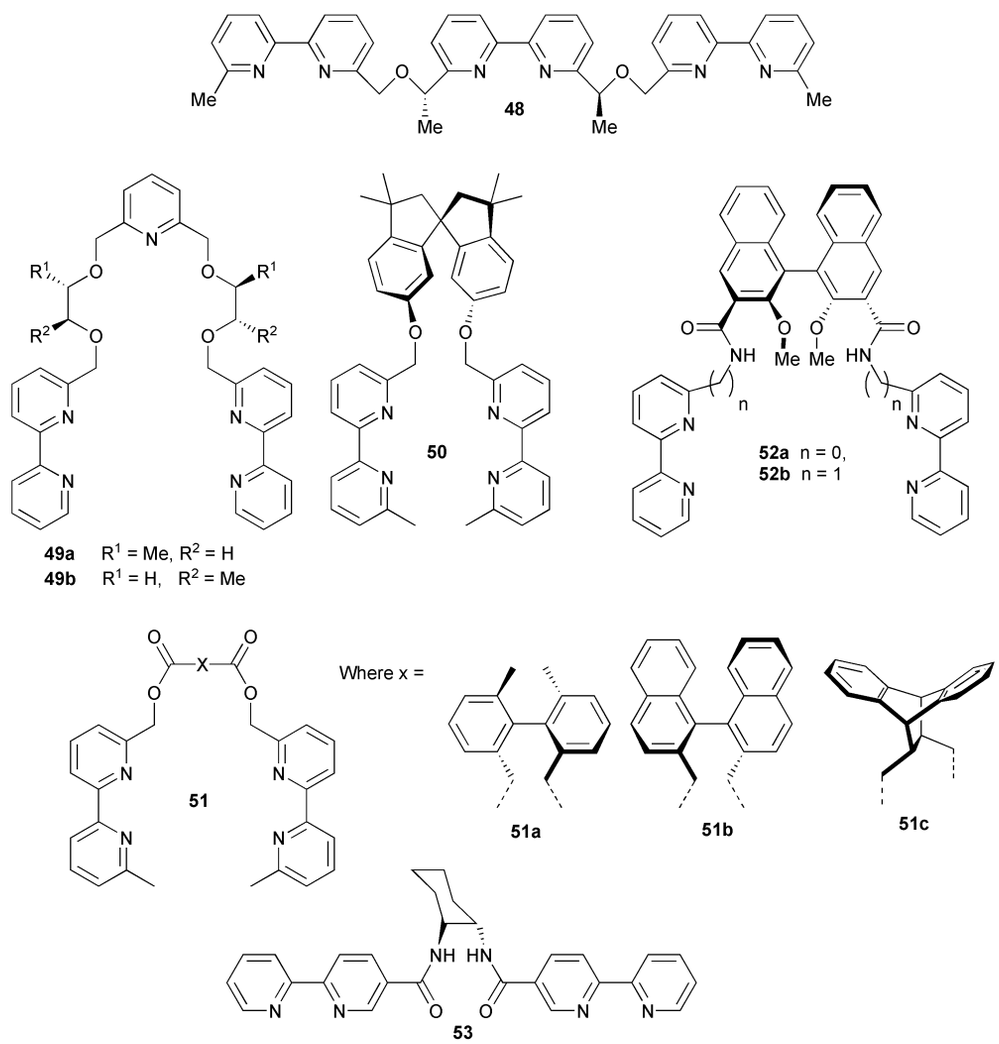
3.1 Metal centred stereochemical control

The primary justification for the synthesis of many 2,2′-bipyridines has been towards the preparation of transition metal complexes. The metal's preferred coordination geometry and the complex's purpose have dictated the substitution pattern of the ligand. This is particularly true with the introduction of enantiopure chiral groups where the desired behaviour is typically governed by the possibility of steric interactions.

3.1.1 6-Functionalized-2,2′-bipyridines

Functionalization at the 6- and 6′-position carbons of the ligand framework (Scheme 1) has been common. This approach has been widely adopted in the preparation of potential asymmetric catalysts where it is important to induce an effect upon other species ligated to the same metal centre through steric interactions. It is these same spatial considerations that have limited their use at metal centres in square-planar and octahedral geometries to the coordination of a single ligand. By way of example, the pinenyl derivatized ligands **15**, **16** and **38** when coordinated to a platinum(II) metal centre have been shown to significantly distort the square-planar geometry towards the less sterically demanding tetrahedral arrangement.[32] As a general rule due to these steric considerations, 6-substituted 2,2′-bipyridines do not form heteroleptic tris-chelate complexes in a pseudo octahedral arrangement or bis-chelate complexes in pseudo square planar geometry but readily assume the less crowded tetrahedral form.

Symmetric bis-chelate pseudo tetrahedral complexes themselves are not chiral, however the use of an unsymmetrical ligand introduces the possibility of mirror images at the metal centre (Fig. 1). The relative orientation of the two ligands creates a helicity defined as Λ (left handed) and Δ (right handed). The control of this chirality has until relatively recently been ignored except in a few unique examples.[12] In



Scheme 13 Bridged 2,2′-bipyridines **48**–**53** possessing chiral spacer groups.

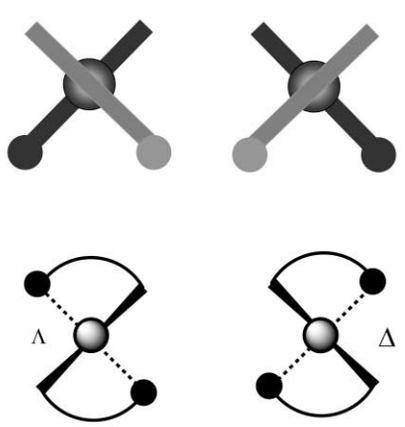


Fig. 1 Schematic illustration of the Λ and Δ helicity introduced in tetrahedral bis-2,2′-bipyridine complexes with asymmetric ligands.

Fig. 2 Schematic illustration of a Λ–Λ dinuclear double stranded helicate.

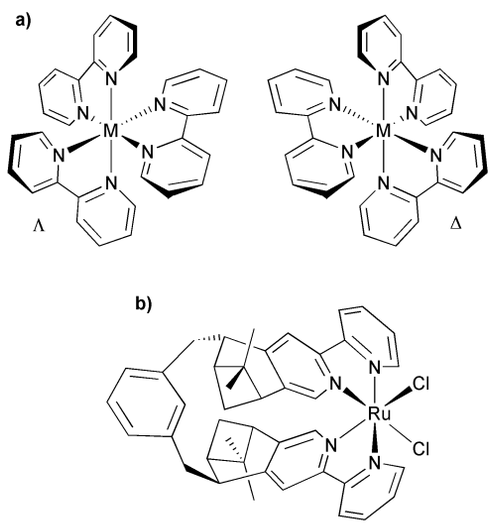
order to predetermine the relative orientation, chiral ligands offer opportunities to dictate the helicity at the metal centre. Early examples have relied upon linked chelating ligands to prepare simple oligonuclear systems or "helicates" as they have commonly become known (Fig. 2).[86,87] Lehn and co-workers successfully demonstrated the control of three tetrahedral copper(I) centres generating a double stranded trinuclear helicate *via* a self-assembly mechanism with **48**.[80] Along similar lines, ligand **46** has demonstrated considerable potential in controlling dinuclear silver(I) chiral architectures, yielding the product as a single enantiomer.[76]

The structural control of mono-nuclear tetrahedral complexes has been achieved in a number of systems using the 2,2′-bipyridine framework. If two of these bidentate units are connected at the 6-position by a rigid chiral spacer, the two chelating moieties are orientated to form a cavity with a predetermined helicity suitable for metal coordination. Cozzi and Siegel published examples with **50** and **51a**–**c**.[82,83] Along with the illustrated ligand systems (Scheme 13) they used in the structural control of mononuclear complexes, they also report di- and trinuclear helicates prepared by the inclusion of additional bipyridine ligands attached at the 6′-position.[82,83] By

limiting the length of the bipyridine–bipyridine linkages, the chirality of subsequent metal centres is controlled by the one adjacent to it, and ultimately from the chiral linkage (X). Along similar lines, the control of the helicity in a number of other mononuclear tetrahedral coordination geometries has been described using ligands **45**[62] and **52**.[84] In an unusual example recently published by von Zelewsky, ligand **16i** forms a distorted tetrahedral environment with copper(I) by coordination of the two olefin groups. Due to the chirality of the ligand, a single helical enantiomer was isolated.[38]

3.1.2 5-Functionalized-2,2′-bipyridines

The use of 5- and 5′-substituted 2,2′-bipyridines has not generated the attention that functionality at other positions has received. However, this position induces steric interactions that can be used to control the stereochemistry of the widely explored tris-chelate pseudo octahedral geometry. This very common metal coordination architecture possesses an inherent helicity (Scheme 14a) which until relatively recently has not been



Scheme 14 **a**) The Λ and Δ helicity introduced in pseudo-octahedral tris-2,2′-bipyridine complexes, **b**) the chiral induction of ligand **44d** to the metal centred helicity in [Ru(**44d**)Cl_2].

systematically investigated[11] despite having been identified by Werner over a century ago.[88] The use of non-racemic 5-functionalized bipyridine systems towards this objective has only just been realized and the number of examples where the individual metal's stereochemistry has been selectively isolated remains small.

As with the oligonuclear double stranded helicates discussed above for metals taking a tetrahedral coordination geometry, 5-functionalized systems have given rise to the preferential formation of triple helicates by combining labile metal cations such as iron(II) and zinc(II) with ligands **44**, **47**[77,78,89] and **53**.[85] Recent studies appear to indicate that the efficacy of the chiral induction at the two metal centres is heavily dependent on the nature of the chiral spacer used. In order to ensure a significant transference of the chirality from the ligand to the two metal centres, rigid and sterically hindered linkages between the two chelating bipyridine ligands are required and is currently the subject of ongoing studies in our research group.

The control of mononuclear species has also been explored using the bridged pinenyl-based "chiragen" system **44** (Scheme 12) with both ruthenium(II) and osmium(II).[72,90,91] Using larger spacer groups such as *meta*-xylyl or hexyl between the two chelating bipyridine moieties such as in **44c** and **d** respectively, the ligand can bind to a single metal centre in a tetradentate configuration (synthesized under high dilution conditions) (Scheme 14b). On account of the two sterically demanding pinenyl groups, the ligand can only adopt one diastereoisomeric form, and thus the helicity of the metal centre is determined by the ligand's chirality. More recently, two more examples of chiral induction using appended amino acids at the 5-position of the 2,2′-bipyridine framework have allowed tris-chelate non-racemic iron(II) complexes to be prepared using a self-assembled synthetic route with ligands **21** and **24**. In both of these latter two examples, a combination of steric interactions and preferential hydrogen bonding gives rise to a predominant diastereoisomer being observed by circular dichroism spectroscopy.[46,51]

3.1.3 4-Functionalized-2,2′-bipyridines

In general, ligands sporting functionality at the 4- and 4′-positions of the 2,2′-bipyridines have the appended groups pointing away from the metal centre giving rise to sterically undemanding species. As a consequence they have little or no effect on the coordinated metal centres stereochemistry (although it can aid in diastereoisomeric separation) and so there are few examples. Ligands **22** and **23** have been used in the preparation of the pseudo-octahedral ruthenium(II) complex $[Ru(L)_3]^{2+}$, giving rise to two diastereoisomers, which were isolated by selective crystallization. These complexes show stereoselective interactions with other species in solution. For example, the tris-chelate ruthenium(II) complexes of **22a**,**b** and **23** have been used in the stereochemical photocatalytic reduction of racemic tris(acetylacetonato)cobalt(II) allowing "deracemerization" and enantioselective oxidation of 1,1′-bi-2-naphthol.[47,48,50,92–101] Alternatively ligand **23**, bound to ruthenium(II), has demonstrated differential secondary coordination to chiral carboxylates through hydrogen bonding.[49]

3.2 Compounds designed for asymmetric catalysis

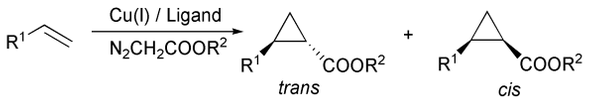
Transition metal complexes have played a pivotal role in the development of homogeneous catalysis. While the chemistry of interest is occurring at the metal centre through metal–carbon and -hydride bonding, most active catalysts contain co-ligands, often misnamed "spectator" species. These ligands play a vital role in the action of the catalyst by activating the bound substrate and imposing asymmetric behaviour.[102] Phosphorous donor systems have been the primary focus in the preparation of these co-ligands, however in many examples such as those listed below, chelating nitrogen donors not only offer an alternative approach but in many cases more active catalysts.[102]

As illustrated in the brief review in 1991 by Bolm,[103] non-racemic chiral bipyridines have demonstrated considerable potential as catalysts in a number of asymmetric reactions. As a general rule, 6-functionalization is preferable, as it not only confers chirality on the metal centre, but also upon other ligated species. In addition, it restricts the direction of approach of reagents required during the reaction.

3.2.1 Asymmetric cyclopropanation of alkenes

The asymmetric synthesis of cyclopropanes from alkenes by the addition of a carbene (typically derived from a diazo compound) upon a copper(I) catalyst is among the earliest examples of enantiomeric homogenous catalysis,[104] and yet continues to receive much attention.[105,106] The reaction leads potentially to two geometric isomers (*trans* and *cis*) each of which exists as a pair of enantiomers. As a consequence, the catalyst needs to control not only the stereochemistry, but in addition the *cis*/*trans* isomerism.

Initial studies with compound **12** demonstrated considerable promise, with a resulting *trans*/*cis* ratio of 86 : 14 in favour of the *trans* isomer and an enantiomeric excess (ee) of 92% using styrene and the *tert*-butyl diazoester (Scheme 15).[30] The results proved comparable to the widely explored semicorrine ligands developed by Pfaltz,[105,106] and ligand **12** was subsequently used as a cyclopropanation agent in the preparation of *trans*-whisky



Scheme 15 Cyclopropanation of alkenes on copper(I).

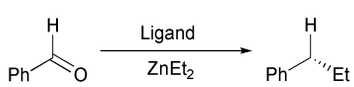
lactone.[30] The catalysis is believed to occur on a copper(I) centre. While many of the nitrogen ligand systems have been explored in this reaction, bipyridines generally stabilize the lower oxidation state, removing the necessity to add a reducing agent to activate the catalyst.[19]

Following the competitive results demonstrated by ligand **12**, a large number of other chiral 2,2′-bipyridine ligands have been studied with differing levels of success. Ligand **1b** was used with a mixture of substrates demonstrating similar product selectivity with styrene to that of ligand **12**. However, the ligand did show considerable dependence on the functionality of the substrate.[19] The bulky ligand **10** demonstrated a respectable formation of 86% for the *trans* isomer (86% ee) with styrene[26] while bis-ferrocene ligand **11** has reached a *trans* selectivity of 97% (87% ee).[27] By examining studies with the pinenyl substituted ligands **15**, **16**, **35** and **36** it is apparent that the C_2-symmetric system gives rise to a better product selectivity, generally in favour of the *trans* isomer.[34,37,107] In addition, the size of the groups attached at the chiral centre adjacent to the pyridine ring (in ligand systems **12**, **16** and **33**) appear to have a considerable influence on the ee, with better results being obtained by large and bulky substituents.

3.2.2 Asymmetric alkylation of aldehydes

The dialkylzinc addition to aldehydes is one of the most extensively studied enantioselective catalytic reactions since its initial report by Oguni and Omi.[108] In a recent review, Pu and Yu describe almost 500 amino alcohol ligand systems with catalytic activity.[109] Curiously, pyridyl alcohols, including the bipyridine systems described in this report indicate a non-linear relationship between the optical purity of the ligand and the product of the reaction.

Using the diol substituted C_2-symmetric 2,2′-bipyridine **1a**, Bolm *et al.* described the zinc mediated alkyl transfer to benzaldehyde (Scheme 16) with almost complete transfer of the



Scheme 16 Addition of diethylzinc to aldehydes.

chiral integrity (97% ee).[16,18,53] The analogous C_1 system **25** demonstrated similar behaviour with only a small decrease in the ee (86%).[18] Collomb and von Zelewsky demonstrated comparable results with the ligand system **35**, and they illustrate the necessity to have bulky substituents to achieve reasonable product selectivity.[63] Recently, Kwong has reported similar results with the C_2-symmetric species **2**–**4** with ees of up to 95% under the same conditions.[20,21]

3.2.3 Asymmetric hydrogenation and hydrosilylation

Chiral diimine ligands have been investigated with respect to hydrogen transfer to ketones offering an alternative to direct hydrogenation with H_2.[110] As early as 1986, ligands **30** and **33** were investigated as potential catalysts on rhodium(I) in the asymmetric reduction of acetophenone by hydrogen transfer from isopropanol, but the turnover of the catalyst and the ee of the product was extremely poor.[55] Better results were obtained by the structurally similar difunctionalized 1,10-phenanthroline ligands.[111] Subsequent to these studies, this reaction has not received much attention although recently, Moutet *et al.* has been investigating the action of rhodium(III) complexes with ligands **34**, **35a** and **44d** in electrocatalytic hydrogenation reactions.[112] While their results indicate that the catalytic procedure is a promising new technique, the asymmetric induction is disappointing.

Using similar conditions to those explored for hydrogenation on rhodium(I), bipyridine **33** has demonstrated promising results in the asymmetric hydrosilylation of acetophenone (Scheme 17).[55] The reduced product was obtained in good yield

Scheme 17 Hydrosilylation of aldehydes on rhodium(I).

and a reported ee of 72%. Under comparable conditions, the C_2-symmetric system **18** demonstrated similar ee.[43] By coordinating the ligand to rhodium(III) forming the complex $[Rh(L)Cl_3]$ before introduction to the reaction, the ees were improved to 90% while at the same time limiting the production of a silyl enol byproduct.[43] It should however be pointed out that ligands **6** and **35** gave very poor asymmetric induction in the reaction.[107]

Both hydrogenation and hydrosilylation reactions appear to rely upon a penta-coordinate transition metal resting state (Fig. 3),[102] with the exception perhaps of ligand **18**. This intermediate

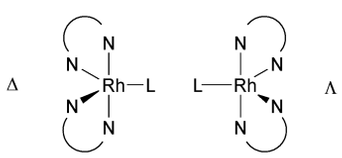
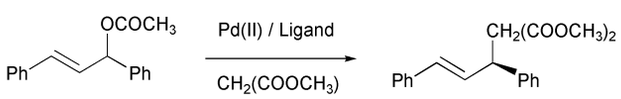


Fig. 3 The possible active catalyst, illustrating the possibility of metal centred chirality.

possesses metal centred chirality, in addition to that of the ligand. This chirality at the reaction centre probably dominates the asymmetric induction in the product to a greater extent than the co-ligand. Once this has been taken into consideration, it is anticipated that some of the more recent ligand systems could potentially improve upon the results described here.

3.2.4 Asymmetric palladium catalysed allylic alkylation

Allylic alkylations, consisting of the substitution of a suitable leaving group with a carbon nucleophile (Scheme 18), have been



Scheme 18 Allylic alkylation of *rac*-(*E*)-1,3-diphenylprop-2-enyl acetate on palladium(II).

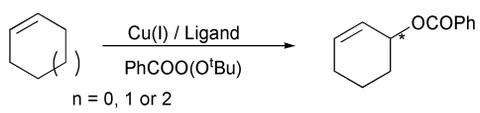
extensively studied due to the importance of carbon–carbon bond formation in organic synthesis.[113] In general, a palladium(0) diphosphine catalyst has been examined, but in the last decade chelating ligands containing nitrogen donors have given significant enhancement in the preparation of a single enantiomer.[102]

In a recent report, Chelucci and co-workers have explored the possible application of a number of the 2,2′-bipyridine ligand systems in the asymmetric catalysed allylic substitution of *rac*-(*E*)-1,3-diphenylprop-2-enyl acetate with dimethyl malonate in the presence of palladium (Scheme 18). Initial experiments with the camphor derived thioether system **7** resulted in an extremely disappointing ee of 48% despite the analogous uncoupled pyridine, bearing the same chiral moiety giving an ee of 79%.[24] Similarly, ligands **30** and **33** demonstrated unremarkable asymmetric induction (0 and 32% ee respectively).[23] However, the fused pinenyl ring C_1-systems of **35** with a large steric bulk adjacent to the 6 position of the 2,2′-bipyridine gave rise

to ees of up to 89%.[64,65] To counter balance this achievement, the inclusion of a sterically demanding group on the opposite side of the ligand system, such as the phenyl substituted **36** caused a dramatic reduction in the chiral induction,[65] and the C_2-symmetric ligand **15** gave rise to an ee of only 22%.[34] It is apparent with this reaction that a C_1-symmetric ligand is preferable as it does not interfere with the approach of the reagents to the metal centre.

3.2.5 Asymmetric allylic oxidation of cycloalkenes

The chiral bipyridine-Cu(I) catalysed allylic oxidation of cyclic alkenes to yield allylic carboxylates, although first reported more than forty years ago (Kharasch reaction[114]), is still one of the few examples of chemical asymmetric oxidation at an allylic carbon atom. This reaction has recently been revisited and developed into a catalytic asymmetric hydroxylation process of cycloalkenes with *tert*-butyl perbenzoate (Scheme 19).[22,34]



Scheme 19 Allylic oxidation of cycloalkenes on copper(I).

To date only the ligands **2**–**5** and **27**–**29** have been examined in this context.[20] However, the degree of stereoselectivity observed (up to 70% ee), stability of the ligands and faster reaction times than published procedures associated with the use of enantiopure bipyridine ligands are encouraging.

3.2.6 Outlook on catalysis

While only a small number of asymmetric catalytic procedures have been investigated in depth, there remains considerable potential for using this most versatile of ligand frameworks in other asymmetric nitrogen based procedures such as the copper(I) olefin aziridination or Diels–Alder reactions.[102] In addition to the traditional asymmetric catalytic procedures, using the rigid framework as a structural motif directing the site of attack, the ligand has the possibility of becoming directly involved in the process. As has already been alluded to, 2,2′-bipyridine is non-innocent (*i.e.* possessing redox chemistry independent of the bound metal ion[115]) and possesses a number of well-explored physical characteristics giving it the possibility to act as a photosensitizer and electron acceptor. As a consequence the parent ligand has been studied both in electro- and photocatalytic systems such as those described by Hamada *et al*.[96,97]

4 Concluding remarks

As a short examination of the current literature illustrates, this diimine framework still possesses considerable potential to introduce non-racemic substituents. Considering the number of recent publications describing the synthesis of new ligand systems, significant progress is anticipated leading to new developments in the structural control of transition metal stereochemistry. For example, a tripodal protein-like system described by Shanzer and co-workers cannot only dictate the helicity but also control the geometric isomerism in tris-chelated systems offering new synthetic opportunities.[116] Furthermore, progress in asymmetric catalytic procedures using both 2,2′-bipyridines and analogous species is predicted. However, the required ligand synthesis is certainly not trivial as this particular report has attempted to illustrate and the synthetic chemists involved in their preparation deserve our admiration. As the non-racemic chiral 2,2′-bipyridines become available to the chemical community, it is anticipated that they will be used in new and varied situations well beyond those covered in this brief tour of the subject, such as chiral shift reagents. Since the parent ligand has been extensively explored with ruthenium(II), due to the unique photophysical behaviour, the development of chiral species offer the possibility of exploring unusual properties such as circularly polarized luminescence. While we can only guess at the future direction of research, the introduction of chirality into this ligand has caused many to take another look at this old friend of coordination chemists.

5 Acknowledgements

I would like to take this opportunity to thank Prof. Alex von Zelewsky for introducing me to these fascinating ligand systems, and Prof Derek Boyd for the productive discussions in the preparation of this manuscript.

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