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The application of molecular tethers in controlling axial chirality

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Abstract: Atropisomeric biaryl compounds are an attractive target in organic chemistry due to their abundance in nature and their utility as ligands in catalysis. Among the methods available for their synthesis, the use of chiral tethers offers very high levels of stereocontrol. In this article, we review the application of molecular tethers in controlling axial chirality across a range of different ligands and natural products.

Keywords: tethers; axial chirality; biaryls; synthesis; stereoinduction.

1. INTRODUCTION

Axial chirality refers to stereoisomerism resulting from the non-planar arrangement of four groups about a chiral axis. Unlike molecules with a tetrahedral centre, this form of chirality results from an axis of chirality and so is most commonly found in biaryl and allene type structures. Axial chirality is usually maintained in molecules *via* bulky *ortho* substituents which prevent rotation around the carbon-carbon bond. Axially chiral structures, or atropisomers, are an important class of compounds. One of the best known atropisomers is BINAP, which has been widely used in asymmetric catalysis as a chiral ligand (Figure 1).[1]

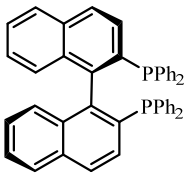


Figure 1. (*R*)-BINAP

Axially chiral structures are also found in nature and often possess interesting biological properties.[2-5] Atropisomers of the same natural product may display radically different activities.[6-8] For example, the dibenzocyclooctadiene steganacin (**1**) was found to be an especially potent antitumor agent with significant *in vivo* activity against P388 leukaemia cells and *in vitro* activity against human throat cancer cells (Figure 2).[9] A key structural feature of steganacin is its axial chirality. The structure-activity relationship of steganacin was investigated by Tomioka *et al.* who concluded that one of the requirements for high bioactivity is an a*R* configuration around the axial linkage.[10] Tomioka determined that the a*R* atropisomer (ED_{50} = < 0.3 μg/mL) is over 58 times more potent than a*S* atropisomer (ED_{50} = < 1.75 μg/mL). There are many other examples of axially chiral biologically active compounds, such as pyrimidol[1,2-a][1,4]benzodiazepine and colchicine, where the configuration around the biaryl linkage has a significant effect on bioactivity.[11-14]

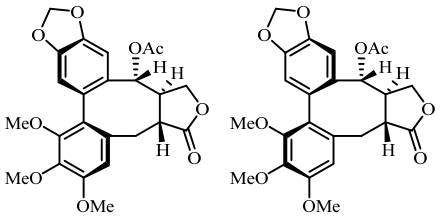
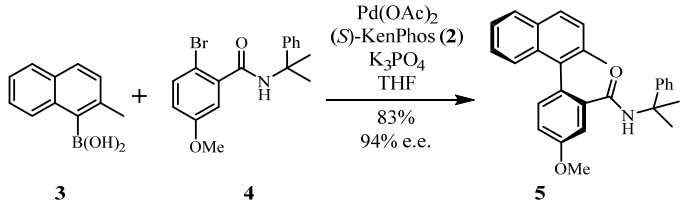


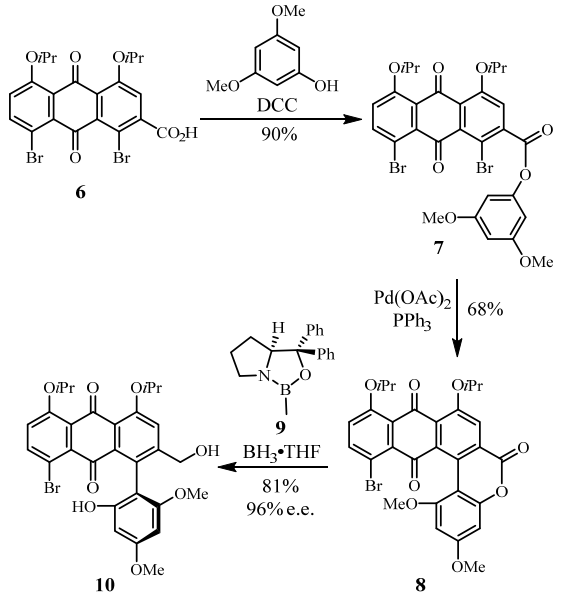
Figure 2. Atropisomers of steganacin

Axial chirality may be controlled *via* a variety of different methods such as the use of chiral auxiliaries, chiral catalysts, the "lactone method" and molecular tethers. Significant advances have been made in recent years in the use of chiral ligands and transition metal catalysts in the stereoselective synthesis of biaryl systems.[15-17] A recent example where chiral catalysts have been successfully employed may be seen in Scheme 1, where (*S*)-KenPhos (**2**) was used as the ligand in the Suzuki-Miyaura cross-coupling of boronic acid **3** with aryl bromide **4** to furnish biaryl **5** with an impressive e.e. of 94%.[18] However, transition metal catalyst systems have the disadvantage of being dependent on the nature of the substrates as well as the proper combination of a central chelating metal with an appropriately designed chiral ligand.[1] This negative aspect of the catalytic approach was highlighted by Guiry who noted that "*research to date highlights the difficulty in finding a "universal" ligand suitable for a wide range of reactions. More commonly, there is a need for tailoring of ligands within each transformation for each substrate used.*"[19]



Scheme 1.

The "lactone method" is a conceptually different approach to the stereocontrolled synthesis of atropisomeric biaryl systems.[20, 21] This method involves the introduction of an ester bridge between the coupling partners, a subsequent intramolecular coupling reaction and resolution *via* a selective lactone cleavage step to afford the desired atropisomer. In some cases, interconversion between the lactone atropisomers facilitates dynamic kinetic resolution and allows for yields above 50% (Scheme 2). However, the "lactone method" has the disadvantage of being dependent on the size of the *ortho* substituents in the molecule and may require recycling of the "wrong isomer" in order to maximise yields.



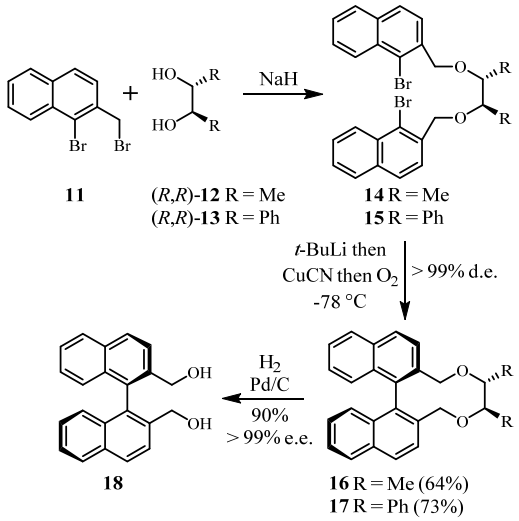
Scheme 2.

Molecular tethers offer an alternative strategy of coupling two aryl units through a fixed chiral bridge and so can ensure transference of the desired chirality around the biaryl axis during the coupling reaction. Thus, tethers offer the advantages of providing access to both homo- and cross-coupled products, of ensuring high stereoselectivity of the desired atropisomer and of being generally applicable. Molecular tethers, therefore, circumvent the requirement to tailor catalysts and ligands to individual reactions. In this article, we will review the application of molecular tethers in the formation of aryl-aryl bonds and in controlling axial chirality.

2. APPLICATION OF MOLECULAR TETHERS

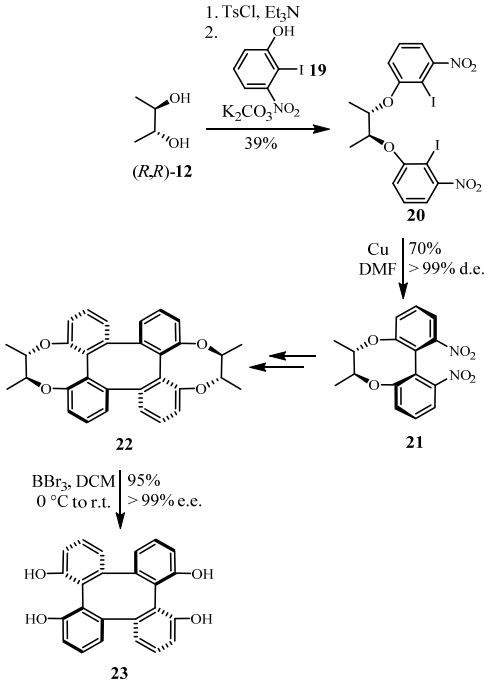
2.1. 1,2-Diol-based tethers

A seminal paper by Lipshutz *et al.* described the stereocontrolled synthesis of biaryls with a variety of 1,2-diol tethers.[22] Two 1,2-diol tethers **12** and **13** were initially tested and were found to give equally good results (Scheme 3). Coupling of two equivalents of benzylbromide **11** with **12** afforded a tethered intermediate which was subjected to copper-mediated oxidative coupling to afford biaryl **16** in 64% yield as a single diastereomer. Hydrogenolysis of the tether furnished target diol **18** in 90% yield with an excellent e.e. of 99%. Similarly high yields and enantioselectivities were reported when tether **13** was employed. The high d.e. of this intramolecular coupling reaction was somewhat surprising given that the formation of a relatively flexible ten-membered ring.



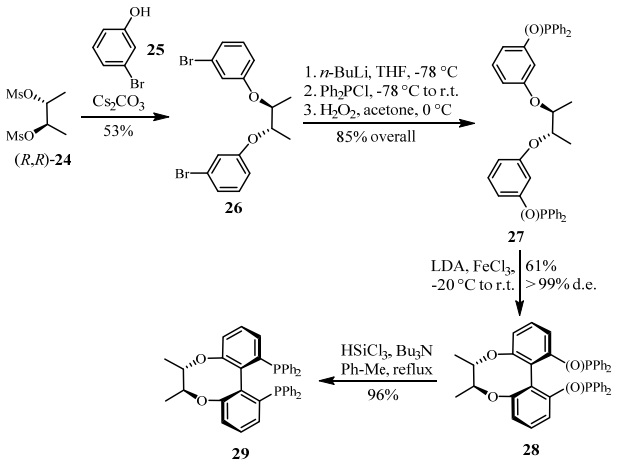
Scheme 3.

In a study of novel 3-dimensional scaffolds composed of hydroxytetraphenylene subunits, Wong *et al.* used diol **12** in the preparation of a key biaryl intermediate (Scheme 4).[23] Diol **12** was initially converted to its bis-tosylate derivate and then coupled to the phenoxide salt of **19** to give aryl iodide **20** in a moderate yield. An intramolecular Ullmann reaction on **20** led to the installation of the requisite biaryl bond and formation of **21** as a single diastereomer in 70% yield. Atropisomer **21** formed the basis for the subsequent construction of tethered tetraphenylene **22**. Cleavage of the tethers was effected by boron tribromide to furnish enantiomerically pure hydroxytetraphenylene **23** in 95% yield.



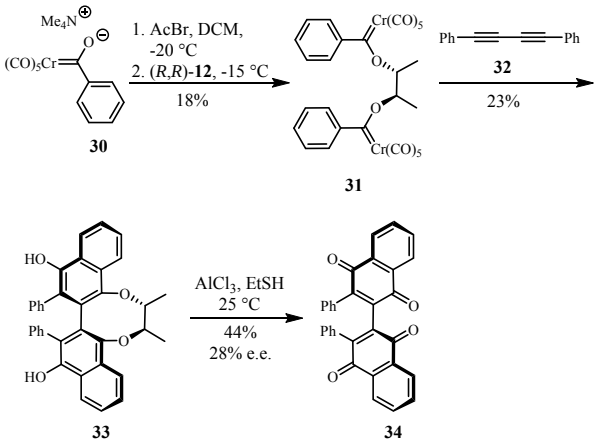
Scheme 4.

Chelating chiral diphosphines are often employed to great success as ligands in organometallic complexes.[24] Qiu *et al.* developed a chiral biphenyl diphosphine ligand **29** and demonstrated its effectiveness in the Ru-catalysed asymmetric hydrogenation of β-ketoesters (Scheme 5). The synthesis began with the bis-mesylate derivative of 2,3-butanediol, **24**, which was coupled to bromophenol **25** to afford aryl bromide **26** in 53% yield. Lithiation, followed by introduction of the phosphinyl groups and subsequent oxidation with hydrogen peroxide resulted in phosphine oxide **27**. Two routes to biphenyl **28** are described by the authors. The first involves *ortho*-lithiation/iodination of **27** followed by Ullmann coupling to produce **28** in 77% overall yield. Alternatively, **27** could be converted directly to **28** by way of an Fe-mediated oxidative coupling in 61% yield. Lastly, **28**, which was recovered as a single diastereomer, was reduced to target diphosphine **29** in 96% yield using trichlorosilane. Interestingly, the tether was not removed in this example but instead incorporated into the ligand scaffold.



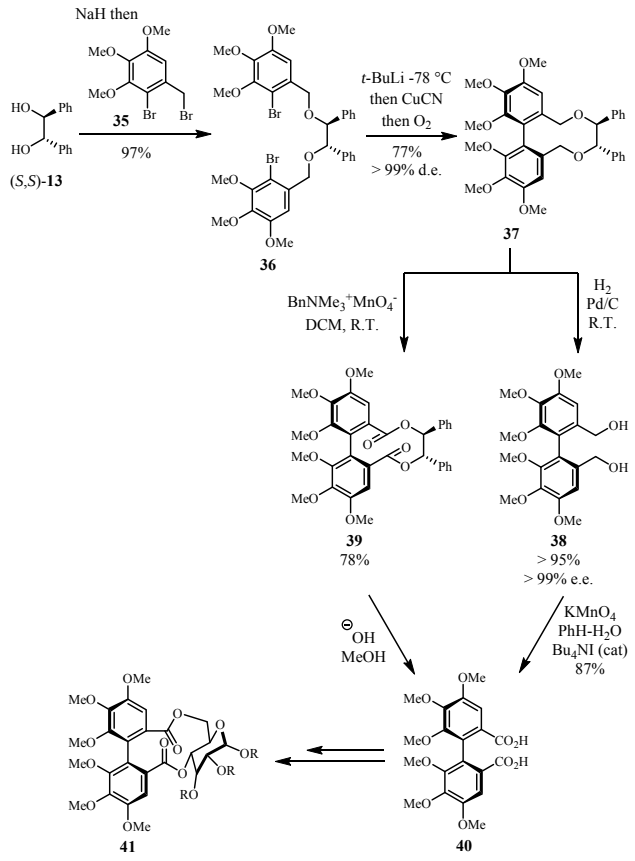
Scheme 5.

Wullf *et al.* have devised a novel stratagem for the construction of biaryl bonds using Fisher carbene complexes and 1,3-butadiynes.[25] By incorporating a chiral tether into this methodology, they have also demonstrated how high asymmetric induction can be achieved in the formation of the biaryl. Accordingly, treatment of metal acylate **30** with acetyl bromide resulted in a mixed anhydride which was combined with tether **12** to afford bis-carbene complex **31** (Scheme 6). The reaction of **31** with butadiyne **32** furnished **33** as the major product in 23% yield. Biaryl **33** was formed as a single diastereomer based on the available ^{1}H and ^{13}C NMR data. Removal of the tether was accomplished by treatment with ethanediol and aluminium trichloride which resulted in the formation of naphthoquinone **34** in 44% yield. The enantiopurity of the compound was determined to be 28% e.e. by optical rotation. The authors believe that partial racemisation occurs during the cleavage of the tether.



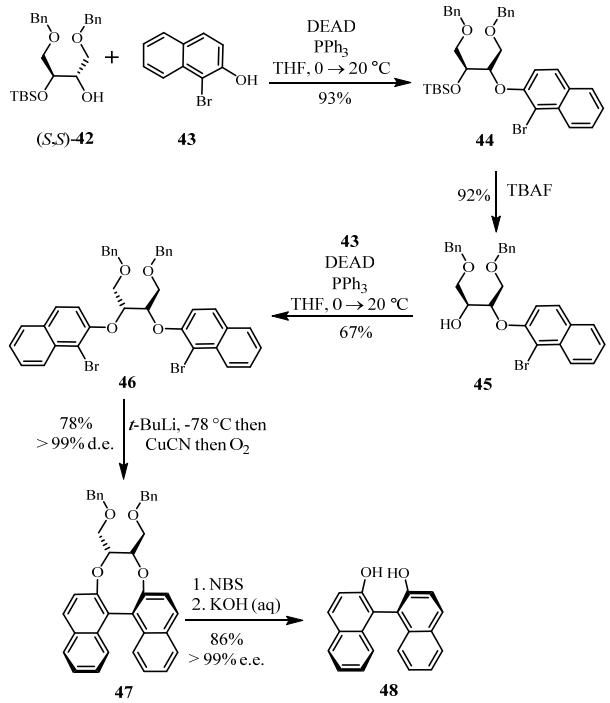
Scheme 6.

Phenyl-based 1,2-diol tether **13** was utilised in the key step of the synthesis of the biologically active natural product tellimagrandin II (**41**) (Scheme 7).[26] The synthetic route revolved around the use of **13** as an effective stereocontroller to facilitate the asymmetric intramolecular homocoupling of aryl halide **36**. Accordingly, diol **13** and benzylbromide **35** were coupled in almost quantitative yield in the presence of sodium hydride to afford bis-ether **36**. Lithiation of this compound with *t*-butyllithium followed by reaction with copper(I) cyanide and oxygen at -78 °C effected intramolecular oxidative coupling to give tethered biaryl **37** in 77% yield as a single diastereomer. Notably, repeating the reaction at a higher temperature of 0 °C led to a 93:7 ratio of isomers. Tether cleavage was then achieved by two different routes. Tether removal was most effective *via* palladium-catalysed hydrogenolysis in methanol which furnished biaryl **38** in almost quantitative yield as a single enantiomer. Alternatively, biaryl **37** could be slowly oxidised over one week to bis-lactone **39** using benzyl(triethyl)ammonium permanganate although the e.e. of this reaction was not reported. Basic hydrolysis of lactone **39** resulted in formation of dicarboxylic acid **40** and also facilitated recovery of the original tether.



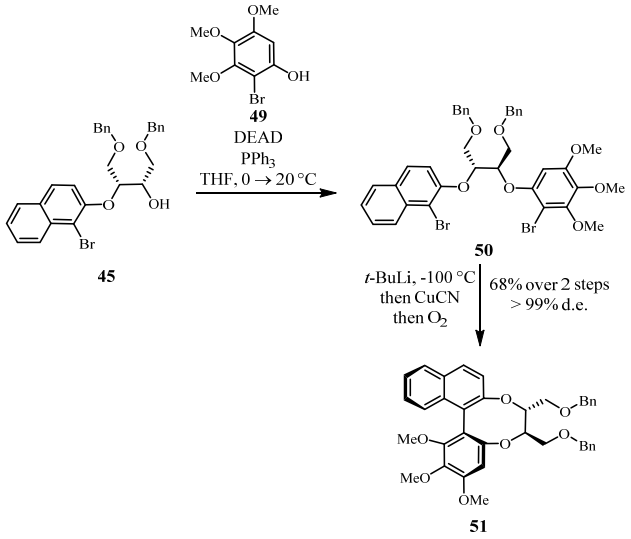
Scheme 7.

To increase the gauche interactions assumed to be responsible for stereoinduction with **12** and **13**, Lipshutz *et al*. prepared protected 1,2-diol **42** from tartaric acid (Scheme 8).[22] Mitsunobu coupling of **42** with **43** afforded **44** in 93% yield which next underwent fluoride-mediated deprotection to **45** with TBAF (tetra *n*-butylammonium fluoride). A second Mitsunobu coupling of **45** with **43** gave intermediate **46** which was then subjected to intramolecular oxidative coupling conditions to produce biaryl **47** as a single diastereomer in 78% yield. A subsequent one-pot double benzylic oxidation reaction using *N*-bromosuccinimide followed by treatment with aqueous potassium hydroxide, successfully removed the tether and gave BINOL (**48**) as a single enantiomer in 86% yield.



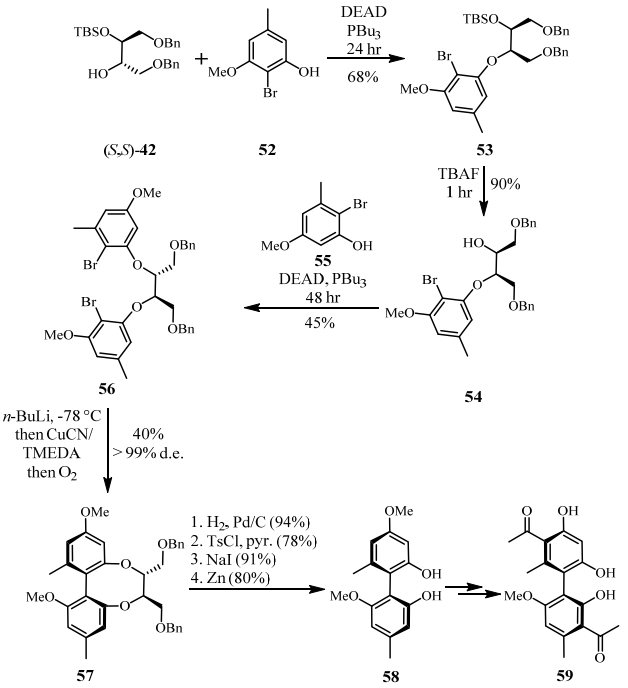
Scheme 8.

Unsymmetrical biaryls could also be produced using this approach by varying the phenolic coupling partners. Starting from common intermediate **45**, initial Mitsunobu coupling with phenol **49** afforded **50** (Scheme 9).[22] Under Lipshutz conditions, the intramolecular cross coupling reaction proceeded smoothly to furnish biaryl **51** as a single diastereomer in 68% overall yield. Only one equivalent of *t*-butyllithium was required to facilitate the intramolecular coupling when the reaction was carried out at -100 °C but 4.2 equivalents of base were required when the reaction was conducted at the higher temperature of -78 °C.



Scheme 9.

Sargent and Kyasnoor also employed protected diol **42** as the stereocontroller for the preparation of **58**, a key intermediate in the synthesis of desertorin C (**59**), a natural product of fungal origin (Scheme 10).[27, 28]The required bis-ether **56** was accessed *via* sequential Mitsunobu couplings of tether **42** with bromophenols **52** and **55**. Oxidative coupling *via* the Lipshutz method furnished biaryl **57** in 40% yield as a single diastereomer. Removal of the tether was achieved in 53% overall yield over four steps. Firstly, removal of the benzyl ether groups *via* palladium-catalysed hydrogenolysis was followed by tosylation of the resultant diol. The bis-tosylate was then converted to the corresponding iodide upon reaction with sodium iodide before reductive elimination with zinc gave the desired enantiomerically pure diol **58**.



Scheme 10.

The authors propose that the aryloxy substituents in **56** adopt a gauche conformation prior to intramolecular oxidative coupling as a result of the anomeric effect, leading to the a*S* configuration of atropisomer **57** (Figure 3).

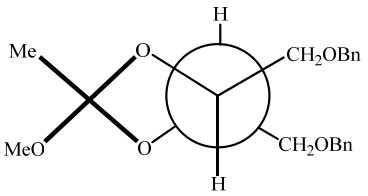
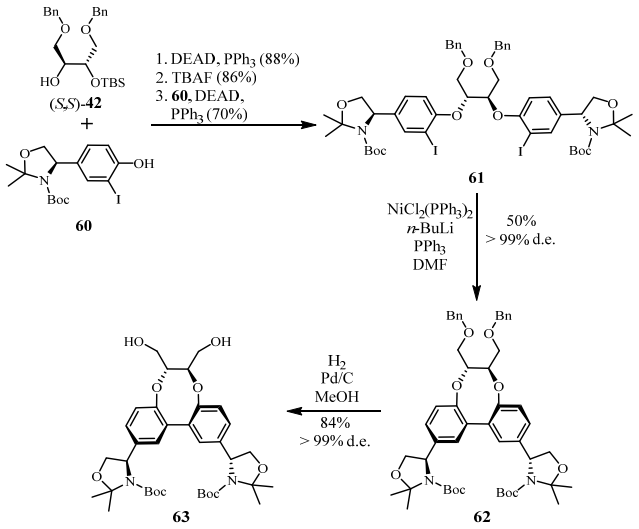


Figure 3. Newman projection of *gauche* conformation of intermediate **56** prior to oxidative coupling

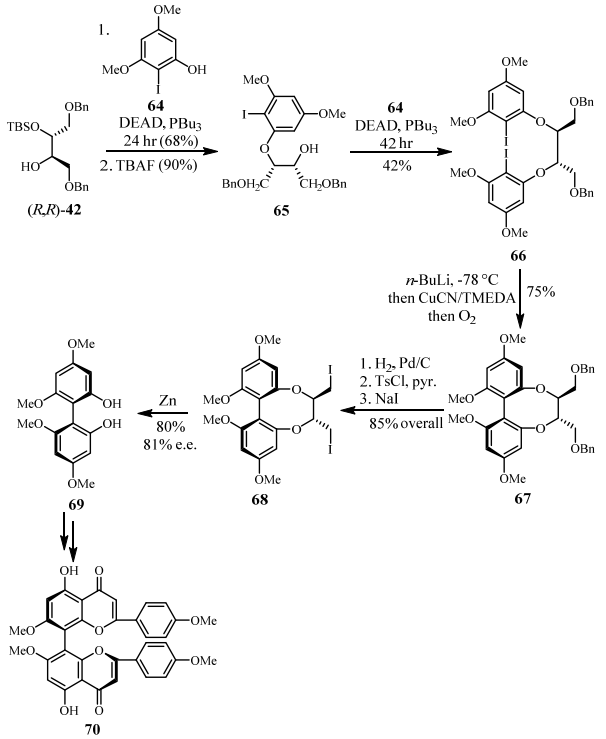
Lipshutz and co-workers reported the successful application of tether **42** in a nickel-catalysed intramolecular homocoupling of aryl iodide **61**, a key step in their synthesis of the anti-bacterial agent vancomycin (Scheme 11).[29] Consecutive Mitsunobu couplings between aryl iodide **60** and **42** afforded bis-ether **61** in 53% overall yield. The authors found that copper-mediated intramolecular oxidative coupling, which had been successful in a previous asymmetric synthesis of BINOL using the same tether, did not afford any of the desired product in this case. Palladium-catalysed Stille or Negishi couplings also returned unreacted starting material. Similarly, preformed Ni(0) failed to effect coupling with the analogous aryl bromide and led to complete reduction of the aryl iodide substrate. Eventually, the authors discovered that repeating the reaction in deoxygenated dimethylformamide with increased loadings of

nickel gave the desired product in 50% yield. Although the yield of the biaryl product was moderate, extremely high atropselectivities (> 99% d.e.) were achieved.



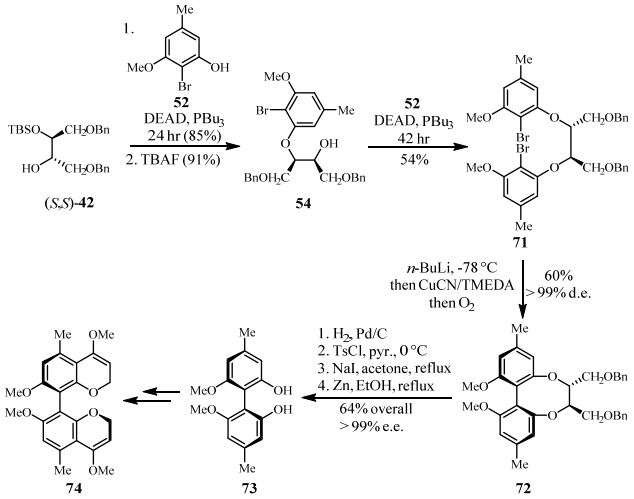
Scheme 11.

The first stereoselective synthesis of the cyclic AMP phosphodiesterase inhibitor 5,5''-dihydroxy-4',4''',7,7''-tetramethoxy-8,8''-bisflavone (**70**) was described by Lin and Zhong (Scheme 12).[30] Having initially found a one-pot double Mitsunobu reactions to produce **66** to be unsuccessful, the authors revised their synthetic strategy and the desired bis-ether **66** was instead accessed by way of sequential Mitsunobu couplings of tether **42** with aryl iodide **64**. The low yield of the tethering steps was ascribed to steric hindrance at the reaction centre. Formation of the biaryl bond *via* an intermediate organocuprate was accomplished in 75% yield, although the d.e. for this reaction was not reported. Cleavage of the tether was then achieved over four steps. Hydrogenolysis of benzyl ether **67**, followed by conversion of the resultant diol to the corresponding bis-tosylate and subsequent treatment with sodium iodide, produced **68** in 85% yield. Reduction of diiodide **68** with zinc powder afforded diol **69** in 80% yield with an *e.e.* of 81%. This compound constituted a key intermediate in the synthesis of bioactive **70**.



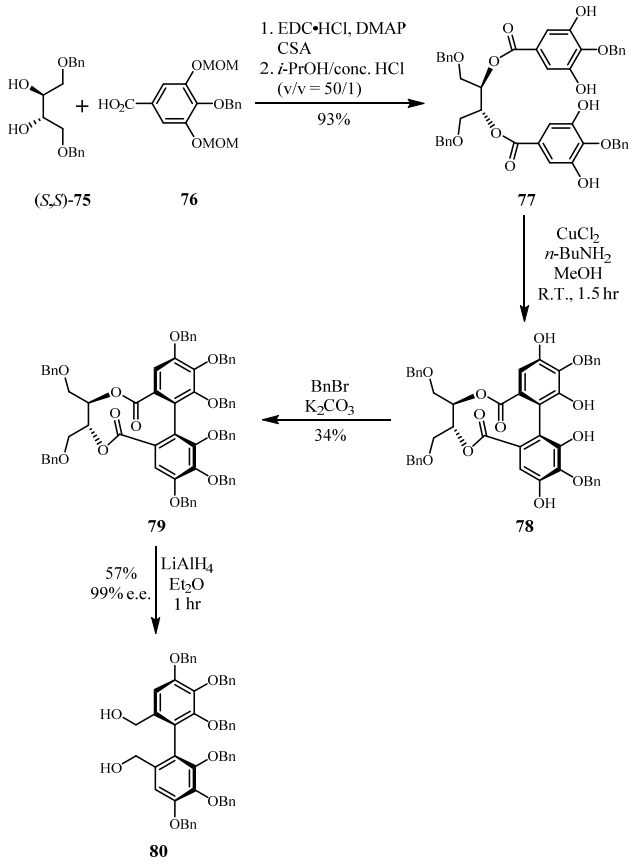
Scheme 12.

The same authors employed a related strategy in their synthesis of the natural product, Kotanin, which was first isolated from *Aspergillus clavatus*.[31] Consecutive Mitsunobu couplings of **42** with **52** afforded aryl bromide **71**, which was subjected to Lipshutz coupling conditions to produce diastereomerically pure biaryl **72** (Scheme 13). Cleavage of the tether followed a similar approach to Scheme 12 i.e. hydrogenolysis, followed by tosylation of the resultant diol, then conversion to the bis-iodide and finally Zn-mediated reduction to furnish **73** as a single enantiomer in 64% overall yield. Further elaboration of intermediate **73** by way of a Fries rearrangement ultimately resulted in the desired target, namely Kotanin (**74**).



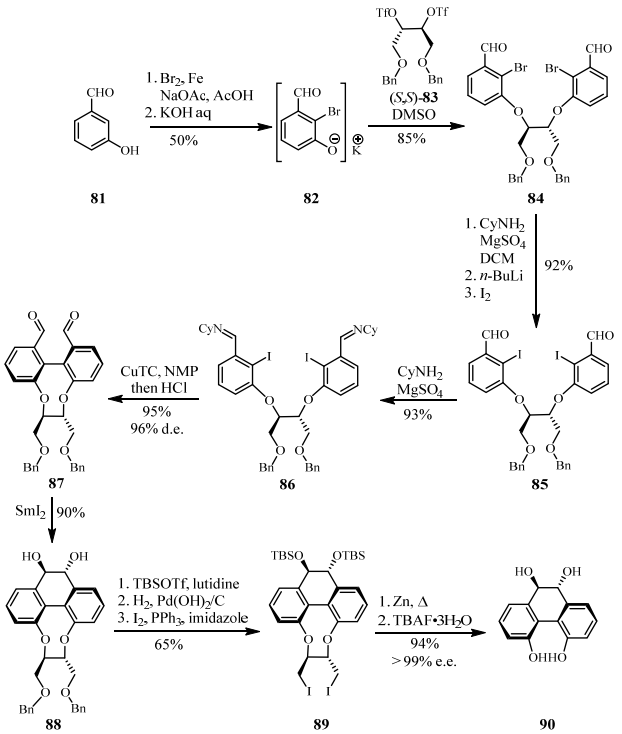
Scheme 13.

The hexahydroxydiphenoyl group is a recurring motif in many natural products as exemplified by the ellagitannins.[32] 1,2-Diol **75** was employed by Asakura *et al.* as a molecular tether in the preparation of a selection of hexahydroxydiphenoyl-containing compounds (Scheme 14). Coupling of diol **75** with carboxylic acid **76**, followed by cleavage of the methoxymethyl ether protecting groups, was achieved in a one-pot two step reaction affording **77** in 93% yield. Intramolecular oxidative coupling, using copper(II) chloride and *n*-butylamine, then produced biaryl **78** with an a*S* configuration after 90 minutes. Biaryl **78** was found to be unstable in air and was used directly in the next step of the synthesis, so neither the yield nor d.e. of this intramolecular coupling reaction was reported. The authors noted that formation of the strained ten-membered ring resulted in a slower overall reaction rate. Biaryl **78** was subsequently converted to hexabenzylated derivative **79** before reduction with lithium aluminium hydride led to cleavage of the tether moiety. Diol **80** was recovered in 57% yield with an e.e. of 99%. Interestingly, the same synthesis carried out with a 1,4-diol tether gave the enantiomeric product (see Scheme 24).



Scheme 14.

In their synthesis of the biaryl core of the antibiotics benanimicin and pradimicin, Breit *et al.* used the ditriflate derivative of **75** as the controlling tether (Scheme 15).[33] Bromination of **81** and conversion to the phenoxide salt was followed by coupling to ditriflate tether **83**, affording **84** in 43% overall yield. Aryl bromide **84** was converted to the corresponding aryl iodide by initial transformation of the dialdehyde to the bis-imine followed by bromine-lithium exchange and finally trapping with iodine and acidic work-up to give dialdehyde **85** in 92% yield. **85** was then tested in a copper(I)-thiophene-2-carboxylate (CuTC) mediated intramolecular coupling reaction, a reagent which allows coupling reactions to be performed under ambient temperatures.[34] However, this approach proved unsuccessful. Conversion of dialdehyde **85** to the corresponding bis-imine **86** and repeating the CuTC-mediated coupling followed by acidic workup afforded the desired biaryl **87** in almost quantitative yield and with a high d.e. of 96%. The chiral tether was removed by cleavage of the benzyl ethers *via* hydrogenolysis with Pearlman's catalyst and subsequent iodination of the resultant diol to afford iodide **89**. Zinc-mediated reductive elimination followed by cleavage of the silylether protecting groups furnished the desired biaryl **90** as a single enantiomer in 94% yield.



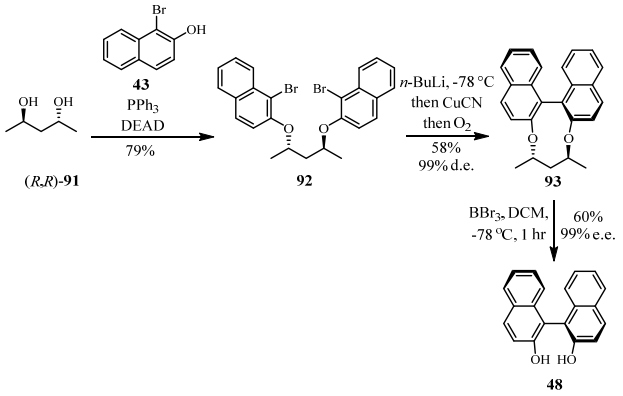
Scheme 15.

2.2. 1,3-Diol-based tethers

Chiral 1,3-diols have also been employed as molecular tethers for controlling axial chirality and have been shown to

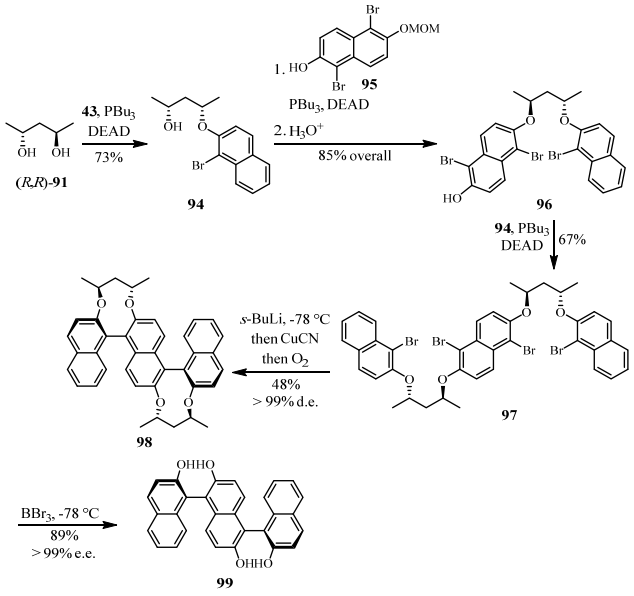
impart a high degree of stereoselectivity during intramolecular coupling reactions.

Sugimura has pioneered the use of 2,4-pentanediol as a chiral tether in the stereoselective synthesis of several atropisomeric compounds, including BINOL.[35] He proposed that 2,4-pentanediol could act as a molecular linker that would be sufficiently flexible to bring both bulky naphthol units close enough to form a new carbon-carbon bond. Sugimura also maintained that the tether would have sufficient rigidity to control the axial chirality around the newly formed biaryl bond. In an effort to test this hypothesis, double Mitsunobu coupling reactions were first attempted which attached two 1-bromo-2-naphthols units (**43**) to 2,4-pentanediol (**91**) affording aryl bromide **92** in 79% yield (Scheme 16). Intramolecular oxidative coupling of **92** produced biaryl **93** in moderate yield and excellent diastereomeric excess. Efforts to improve upon the yield proved unsuccessful. For example, when the coupling reaction temperature was increased from -78 °C to 0 °C, the high stereoselectivity was maintained, but the yield dropped to 49%. Oxidation of the organocuprate intermediate with ferric acetylacetone instead of oxygen resulted in a poorer yield of 36%. Removal of the tether to furnish BINOL initially proved problematic. Treatment of **93** with aqueous hydrobromic acid in acetic acid at 100 °C led to removal of the tether and the formation of BINOL in low yield (39%) and a relatively poor e.e. (68%). By contrast, the use of boron tribromide at -78 °C allowed for the isolation of enantiomerically pure BINOL in an improved yield of 60%.



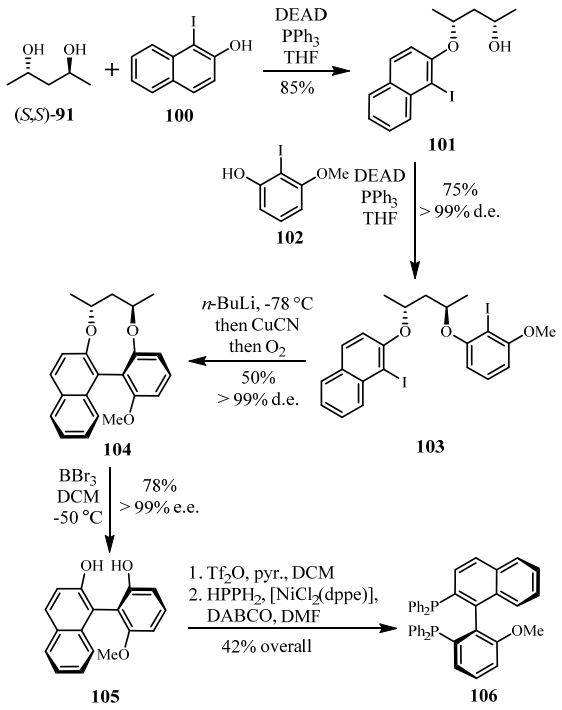
Scheme 16.

Sugimura expanded on this work in a follow-up publication, where he described the synthesis of a novel TERNOL homolog of BINOL (Scheme 17).[36] Consecutive Mitsunobu couplings of tether **91** with **43** and **95**, followed by acid hydrolysis of the MOM-ether protecting group, gave aryl bromide intermediate **96**. Phenol **96** then underwent another Mitsunobu coupling with **94** to furnish tetrabrominated aryl intermediate **97**. A double, intramolecular oxidative coupling of **97** then proceeded under standard conditions affording **98** as a single diastereomer. Cleavage of both tethers was accomplished with boron tribromide, producing enantiopure TERNOL (**99**) in 83% yield.

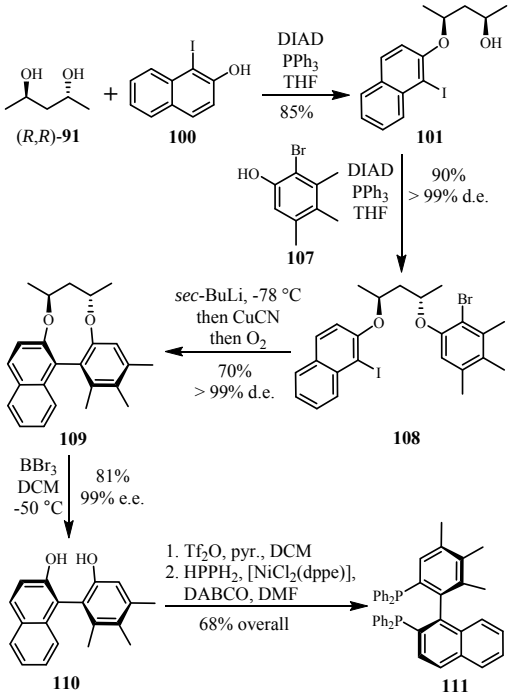


Scheme 17.

Chelating chiral diphosphines are often used as ligands in organometallic complexes.[37] Chiral diphosphine **106** was developed by Marinetti *et al.* for use in the asymmetric Ru-mediated hydrogenation of carbonyl-containing substrates (Scheme 18).[38] Synthesis of **106** began with two successive Mitsunobu reactions of tether **91** with naphthol **100** and phenol **102** respectively affording aryl iodide **103** in 64% overall yield. Copper(I) cyanide-mediated oxidative cross-coupling of **103** then afforded atropisomer **104** in 50% yield as a single diastereomer. Removal of the tether was achieved by dealkylation of **104** with one equivalent of boron tribromide which furnished biaryl **105** as a single enantiomer in 78% yield. The authors noted that employing an excess of boron tribromide led to concurrent cleavage of the methoxy group in the structure. Biaryl **105** was then carried through to the desired diphosphine **106** over two steps. The high stereoselectivities associated with this synthesis made this a viable route for the preparation of these novel chiral ligands.



Scheme 18.



Scheme 19

In later work, Marinetti *et al.* adopted a similar strategy in their synthesis of a napthyl-containing diphosphine ligand. As before, successive Mitsunobu coupling of **91** with **100** and **107** afforded tethered intermediate **108** (Scheme 19).[39] Formation of the biaryl bond proceeded with excellent diastereoselectivity giving **109** in 70% yield. Removal of the tether was accomplished with boron tribromide, producing atropisomer **110** in 81% and 99% e.e. Further elaboration of **110** resulted in target diphosphine **111** which was found to successfully promote asymmetric Ru-catalysed 1,4-additions of boronic acids to unsaturated ketones.

Zhang *et al.* have prepared a library of C3-TunePhos ligands all having the same general structure as outlined in Figure 4.[40-44] In each case, tether **91** was employed as the key stereocontroller for the formation of the biaryl axis and the tether was itself incorporated into the ligand scaffold. These ligands were subsequently tested in Ru-catalysed asymmetric hydrogenations on various substrates including α-keto esters, β-keto esters and α-dehydroamino acid methyl esters.

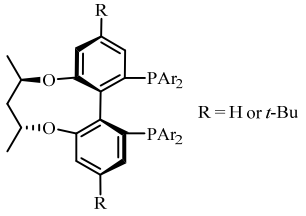
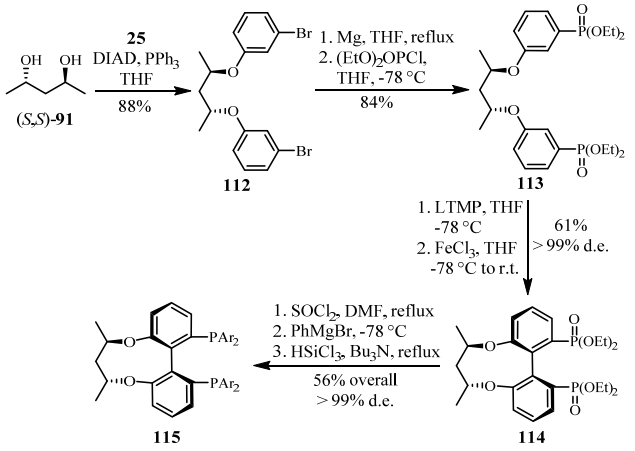


Figure 4. General structure of diphosphine ligands prepared by Zhang *et al.*

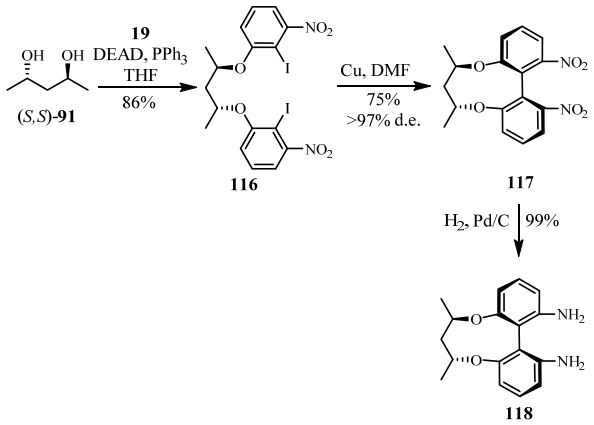
A typical synthetic route is outlined in Scheme 20. Bis-ether **112** was prepared *via* double Mitsunobu reactions of **91** with **25**. Conversion of aryl bromide **112** to the corresponding Grignard intermediate and quenching with diethyl chlorophosphate afforded phosphate **113** in 84% yield. A sequence of thermodynamically controlled *ortho*-lithiation with LTMP (lithium 2,2,6,6-tetramethylpiperidide) and subsequent Fe(III)-mediated oxidative homocoupling furnished **114** as a single diastereomer in 61% yield. Finally, addition of phenylmagnesium bromide to the phosphonic dichloride derivative of **114**, followed by reduction of the

resulting phosphine oxide with trichlorosilane, afforded the target ligand **115** in 56% overall yield.



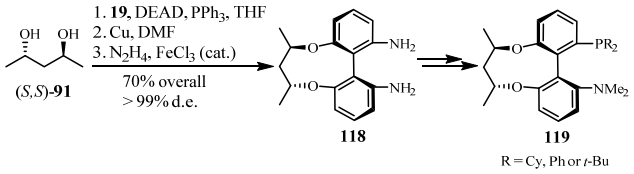
Scheme 20.

Wang *et al.* synthesised several diamine ligands again relying on tether **91** to control the axial chirality (Scheme 21).[45] Double Mitsunobu reactions of **91** with **19** proceeded smoothly to afford **116** in 86% yield. Intramolecular, copper-mediated Ullmann coupling of **116** furnished **117** in 75% yield and 97% d.e. The aromatic nitro-groups were reduced *via* palladium-catalysed hydrogenation to afford target diamine ligand **118** in almost quantitative yield.



Scheme 21.

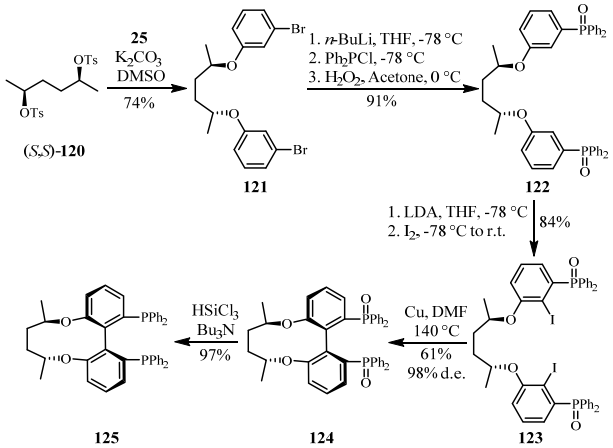
Qiu *et al.* have developed a series of P,N-ligands which were found to successfully promote Pd-catalysed asymmetric Suzuki-Miyaura coupling reactions.[46] The installation of the biaryl axis mirrors the approach taken by Wang using tether **91** as the stereocontroller, and with diamine **118** serving as a common intermediate (Scheme 22).



Scheme 22.

2.3. Other diol-based tethers

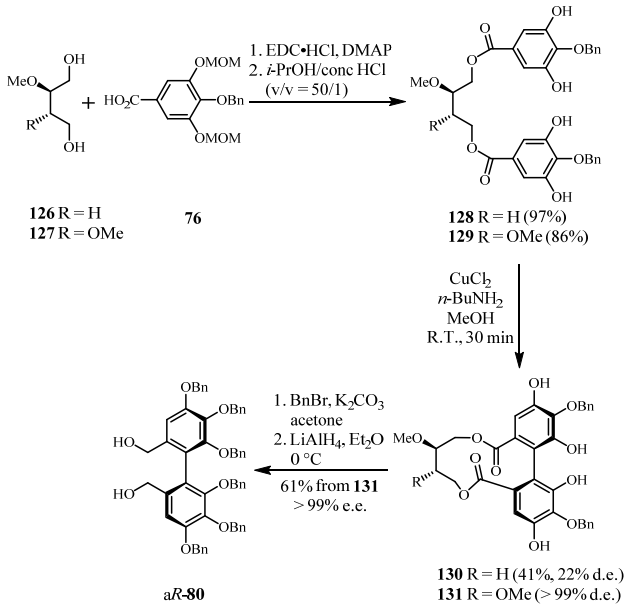
In their study of chiral-bridged diphosphine ligands, Qiu *et al.* prepared a sequence of compounds utilising 1,2-, 1,3- and 1,4-diol tethers which were incorporated into the final ligand framework.[47] The synthetic route is similar to that described in earlier work (e.g. Schemes 5 and 22) and is outlined in Scheme 23. Reaction of bis-triflate **120** with **25** furnished aryl bromide **121** in 74% which was converted to phosphine oxide **122** over 3 steps. Aryl iodide **123** - prepared by way of *ortho*-lithiation of **122** and subsequent iodination – was subjected to Ullmann coupling conditions to install the biaryl bond, affording **124** in 61% and a high d.e. of 98%. The diastereoselectivity observed for the 1,4-diol tether compared favourably with the 1,2-diol tether (> 99% d.e.) and the 1,3-diol tether (> 99% d.e.). However, the yield of the biaryl product was lower when measured against both the 1,2-diol (91%) and the 1,3-diol (71%).



Scheme 23.

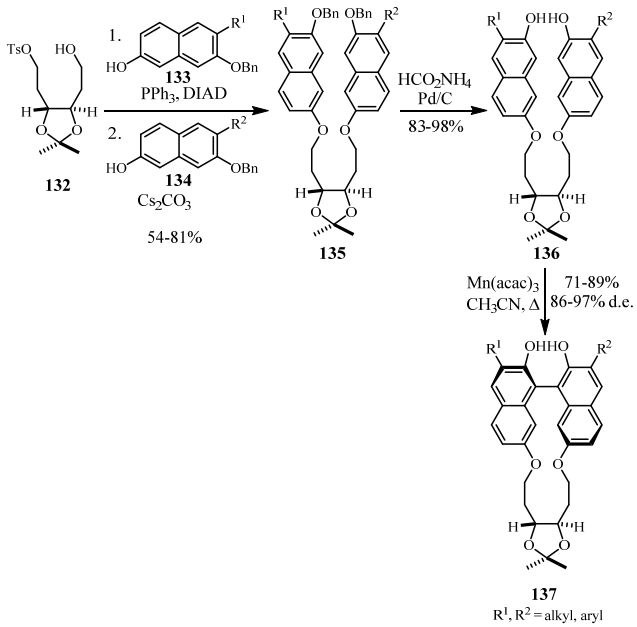
We have previously discussed the work of Asakura *et al.* which exploited a 1,2-diol tether to install a biaryl bond with an a*S* configuration in a series of hexahydroxydiphenoyl compounds (see Scheme 14). By switching to a 1,4-diol tether, the authors were also able to successfully synthesise the target biaryl with the opposite a*R* configuration.[32] Two different 1,4-diols were tested in this study, namely monomethoxy-substituted **126** and dimethoxy-substituted **127** (Scheme 24). The esterification of carboxylic acid **76** with 1,4-diols **126** and **127** proceeded smoothly to give bis-esters **128** and **129** in high yields (Scheme 24). Subsequent intramolecular coupling using copper(II) chloride proceeded

quite rapidly and this is believed to be as a result of the formation of a mildly strained 12-membered cyclic product. Interestingly, when using **126** (R = H) as the controlling tether, **130** was recovered as a mixture of diastereomers with a d.e. of only 22%. By contrast, use of **127** (R = OMe) as the tether resulted in the formation of **131** as a single diastereomer. The authors ascribe the higher atropselectivity to the increased *gauche* steric hindrance present in **129** as it undergoes oxidative coupling.



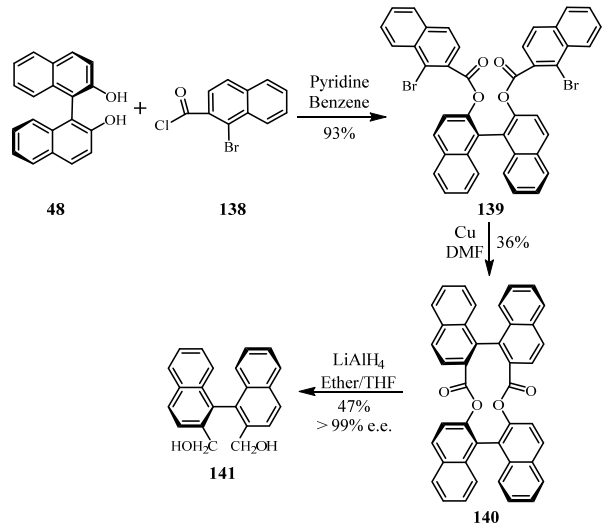
Scheme 24.

Lipshutz developed an alternative diol-based tether, **132**, for the construction of atropisomeric cyclo-BINOLs (Scheme 25).[48, 49] Tether **132**, which could be prepared from *E*-β-hydromuconic acid by way of a Sharpless asymmetric dihydroxylation, underwent Mitsunobu coupling with naphthol **133**. Reaction of the resultant tosylate with **134** in the presence of cesium carbonate furnish tethered intermediate **135** in yields ranging from 54-81%. Debenzylation of **135** *via* transfer hydrogenation afforded **136**. Treatment of **136** with Koga's reagent effected intramolecular oxidative coupling to give cyclo-BINOL **137**. It was subsequently discovered that the reaction proceeded with higher yields (69-89%) and d.e.'s (84-97%) using 1.2 equivalents of Mn(III) in acetonitrile. Tether **132** was found to be sufficiently general so as to facilitate the intramolecular coupling of a variety of substituted cyclo-BINOLs.



Scheme 25.

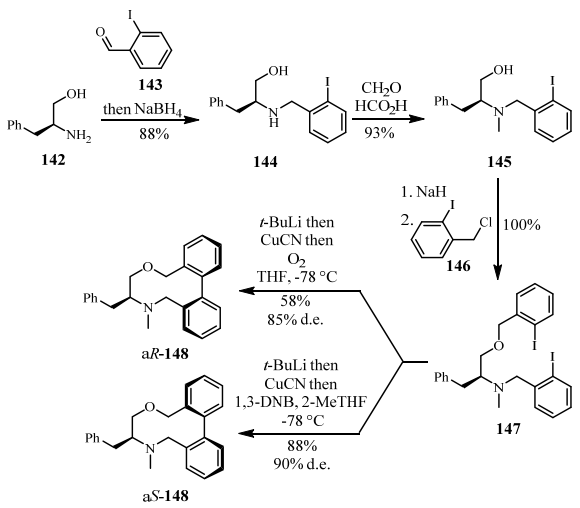
Miyano and co-workers employed enantiopure *R*-BINOL as their stereocontroller for the synthesis of atropisomeric binaphthyls (Scheme 26).[50] Coupling of 1-bromo-2-naphthoyl chloride (**138**) with *R*-BINOL (**48**) produced diester **139** in 93% yield. Diester **139** then underwent Ullmann coupling to furnish tethered-atropisomer **140** in 36% yield along with significant amounts of reduction and oligomeric products. Binaphthyl **140** was determined to be a single diastereomer by HPLC analysis. Removal of the BINOL tether was achieved by reduction of **140** with lithium aluminium hydride which gave the final product **141** in a moderate yield of 47%. Target **141** was found to be enantiomerically pure based on its specific optical rotation and by derivitisation to the corresponding Mosher's esters.



Scheme 26.

2.4. Amine-based tethers

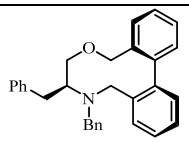
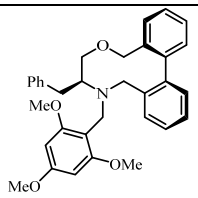
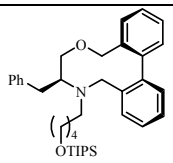
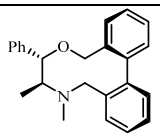
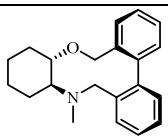
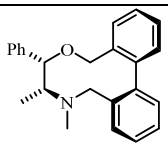
Chiral amine-based tether **142** has been developed by Schreiber *et al.* for the asymmetric synthesis of biaryls incorporating nine and ten-membered rings (Scheme 27).[51] Attachment of the tether was achieved by condensation of amine **142** with 2-iodobenzaldehyde (**143**) and reduction of the resultant imine with sodium borohydride to furnish **144**. Methylation of secondary amine **144** was followed by alkylation with benzyl chloride **146** to furnish aryl iodide **147**. The resultant iodide was successfully coupled using the Lipshutz method of iodine-lithium exchange, cupration and oxidation to give biaryl **148** in 58% yield. The stereoselectivity of this reaction was relatively moderate with a d.e. of 58% achieved for the desired a*R* atropisomer. Notably, the authors discovered that the choice of solvent, reaction temperature and oxidant all played a crucial role in determining the degree and direction of atropselectivity. Accordingly, optimised conditions, using 2-methyltetrahydrofuran as solvent with 1,3-dinitrobenzene as oxidant and a reaction temperature of -40 °C, resulted in an increased yield of 88% and d.e. of 90% but with the opposite configuration at the biaryl axis.



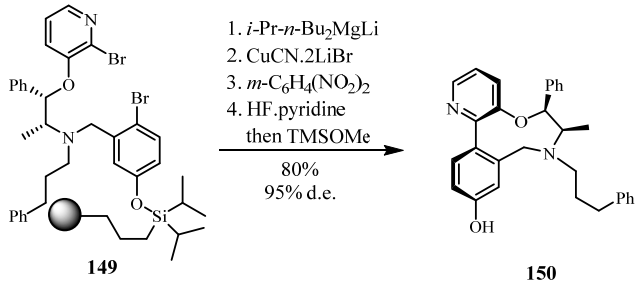
Scheme 27.

Several variations of tether **142** were also tested and generally found to display comparable or lower diastereoselectivities (Table 1). In all cases, the tether was incorporated into the final target structure.

Table 1. Comparison of diastereoselectivity of amine-based tethers

Entry	Biaryl	% Yield	% d.e.
1		94	5
2		88	37
3		83	75
4		88	89
5		77	83
6		68	82

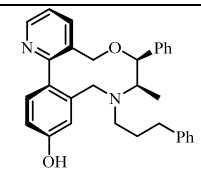
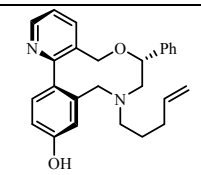
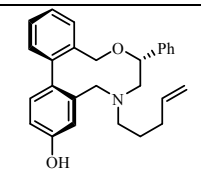
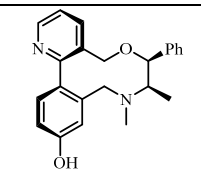
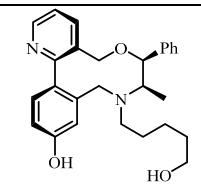
Schreiber further developed this tether family to incorporate solid-phase syntheses.[52] Accordingly, advanced intermediate **149** was converted to biaryl **150** by initial magnesium-bromine exchange followed by magnesium to copper transmetallation and oxidation of the resulting cuprate with dinitrobenzene. Finally, addition of hydrofluoric acid in pyridine released target **150** from the solid phase resin in 80% yield and 95% d.e. The greater rigidity of the 9-membered ring relative to a 10-membered ring means that **150** displays higher conformational stability even though one of the *ortho* substituents on the biaryl nucleus is a nitrogen atom.



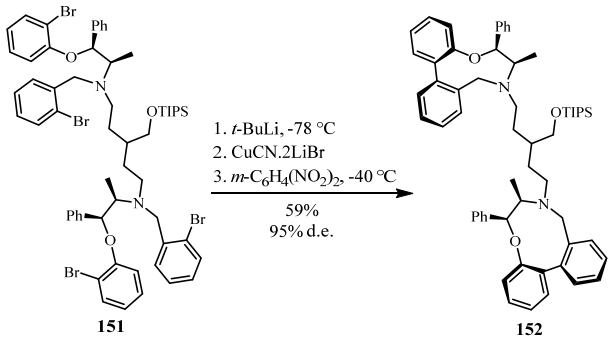
Scheme 28.

Several other amine-based tethers were shown to successfully control atropselective intramolecular couplings, affording nine-membered cyclic products with high diastereomeric excesses (Table 2).

Table 2. Solid phase ring-forming cyclisations with amine tethers

Entry	Biaryl	% Yield	% d.e.
1		80	> 90
2		91	> 90
3		76	> 90
4		58	> 90
5		69	> 90

In the same publication, Schreiber and co-workers performed a double cyclisation on substrate dimeric intermediate **151** to afford the bis-macrocycle **152** in 59% yield with only trace amounts (< 5%) of the mono-cyclised product detected (Scheme 29). The amine tethers exhibited a high degree of stereocontrol and this impressive synthesis afforded the desired product in a d.e. of 95%.

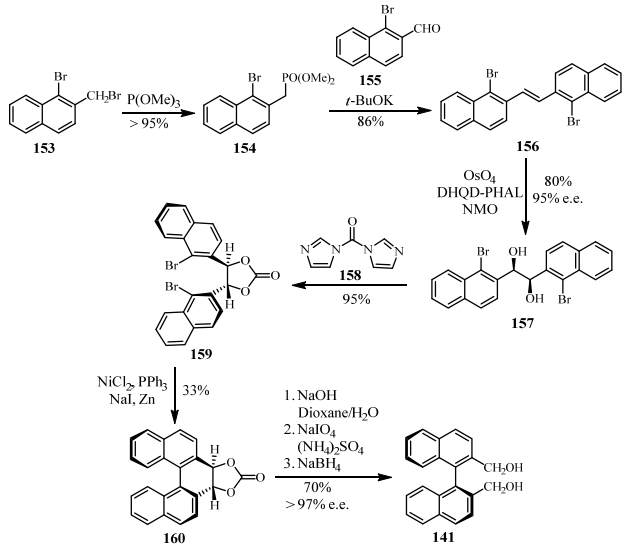


151 **152**

Scheme 29.

2.5. Miscellaneous tethers

Rawal *et al.* reported a hybrid strategy for synthesising axially chiral biaryls whereby the controlling "tether" is derived from the substrate itself and is later removed following installation of the biaryl axis.[53] The synthetic scheme starts with benzyl bromide **153** which is converted to phosphonate **154** *via* an Arbuzov reaction with trimethyl phosphate. Horner-Wadsworth-Emmons reaction of phosphonate **154** with aldehyde **155** affords alkene **156** in 86% yield. Chirality was then introduced into this structure by way of a Sharpless asymmetric dihydroxylation which furnished diol **157** in 80% yield and an e.e. of 95%. In an effort to minimise the available conformations that the product could occupy, diol **157** was converted to carbonate ester **159** in 95% yield upon treatment with carbonyldiimidazole (**158**). Formation of the carbonate ester ring facilitated high atropselectivity in the subsequent intramolecular coupling reaction. The authors reported that **159** was reluctant to undergo intramolecular Ullmann coupling. As an alternative to the Ullmann coupling, the use of Semmelhack's nickel catalyst system[54] afforded biaryl **160** in 33% yield. The linker molecule was then removed by initial hydrolysis to the diol, followed by oxidative cleavage to the bis-aldehyde. Finally, reduction with sodium borohydride afforded the target compound **141** in 70% yield and 97% e.e.



Scheme 30.

3. CONCLUSION

Atropisomeric biaryl compounds are an attractive target in organic chemistry. Among the methods available for their synthesis, the use of controlling tethers offers very high levels of stereocontrol. From this review it is clear that diols, especially 1,2-diols and 1,3-diols, are the most widely employed form of molecular tether in the literature. Such tethers have been successfully employed in both homocoupling and cross-coupling reactions. These diol-based tethers impart a high degree of control over axial chirality during intramolecular coupling reactions, often affording the desired biaryl as a single diastereomer. However, removal of these linker molecules has sometimes proved challenging, and may necessitate multiple low yielding steps.

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