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Abstract

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Keywords

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The first syntheses of enantiopure 2,2'-biindoline†

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The first two syntheses of chiral 2,2'-biindoline are reported either in five steps from 2,2'-bioxirane, or three steps from 2,2'-biaziridine, both with exceptional enantiopurity.

Chiral biamine compounds are well established as ligands in stereoselective metal-catalysed reactions, including allylic additions, reductions and asymmetric dihydroxylations.¹ Our interest in chiral ligand design focusses on a new principle that uses helix sense discrimination to achieve stereoselective outcomes. In particular, ligand types we are interested in include biphosphines, biarsines, biamines and ligands that possess a mixture of heteroatoms. The molecular helix itself is defined by two stereogenic atoms, flanked by metal co-ordinating heteroatoms, manifesting an arc of helicity once bound to a metal *e.g.* palladium. The helical groove depth and degree of twist could be modulated by a range of substituents, including the presence of fused rings. Importantly, an appropriate synthetic strategy towards such structures should not only be highly stereoselective, but should allow articulation to efficiently produce a range of substituted ligands including those with different ring sizes, and/or containing fused ring structures.

One example of a biamine that would meet our helical design criteria when metal-bound is 2,2'-biindoline **1**. Despite the illustrious history of the indoline molecule, including its place in natural product chemistry, drug design and development and its use in industry as a key element in catalysts, there has been surprisingly little investigation into the dimeric structure **1**² – even more surprising is the lack of any reporting of the stereoselective synthesis of **1** or related compounds that contain **1** as a substructure. In our first attempt at a stereoselective synthesis of 2,2'-biindoline **1** using a metathesis–asymmetric dihydroxylation (AD) strategy, poor yields and stereoselective outcomes resulted from steric hinderance in the AD step.³ Therefore, we devised a new strategy to the key intermediate chiral diols (*e.g.* **4**) and in this communication report the first synthesis of the parent 2,2'-biindoline **1** in enantiopure form.

Our chiral pool starting material was the bioxirane (*R,R*)-**3** (Scheme 1), prepared from D-tartaric acid as previously described.⁴ This was ring opened with Grignard **2**⁵ under CuI catalysis,⁴ giving a mixture of diols arising from the

competing mono-addition of the chloride and iodide anions. The desired diol (*R,R*)-**4** was isolated (31%) by selective crystallisation from the crude mixture. This was converted to dimesylate (*R,R*)-**5** (84%) which in turn was subjected to standard azidation conditions, affording – after an extremely sluggish reaction – a crude mixture of the desired diazide (*S,S*)-**6** (~60% conversion) and a chromatographically inseparable azidoalkene arising from mono-elimination (~25% conversion, not illustrated). The diazide was isolated after oxidation of the by-product with KMnO₄ and subsequent silica gel column chromatography (47% yield overall). Staudinger reduction provided complete conversion to the diamine (*S,S*)-**7** which was isolated by successive crystallisation as its dihydrochloride salt and liberation with sodium hydroxide (71%).⁶ Finally, after several unsuccessful attempts to form the biindoline using standard palladium and copper amination protocols, the molecule was found to undergo the desired regioselective cyclisation under microwave irradiation, providing the target ligand (*S,S*)-**1** in 57% yield.⁷ The product was found to be enantiomerically pure (>99% *ee*) after preparing the diBoc derivative⁸ and performing HPLC with analysis relative to a sample enriched in the *R,R*-enantiomer that was previously synthesised in our laboratory using the metathesis – AD strategy.³

Although the synthesis of biindoline (*S,S*)-**1** from bioxirane (*R,R*)-**3** provided the target compound in enantiomerically pure form, the strategy needed to be modified to avoid the low yielding ring opening with Grignard **2** and the inefficient azidation reaction.

Therefore, an alternative synthesis of **1** was proposed using the analogous biaziridine as the chiral building block, such that ring opening would directly install the required nitrogen atoms. This would provide a shorter entry to the penultimate diamine (*S,S*)-**7**, which could be cyclised under the established palladium catalysed microwave conditions.

Efficient ring opening of the biaziridine with Grignard **2** (Scheme 2) would require *N*-protection with an electron withdrawing group and two such derivatives of the molecule are known – the Boc (**8**, R = Boc)⁹ and the tosyl (R = Ts).¹⁰ Given that strong reducing conditions are required to remove the tosyl group in good yield,^{11,12} we chose to begin our investigations with the acid labile Boc carbamate as the protecting group.

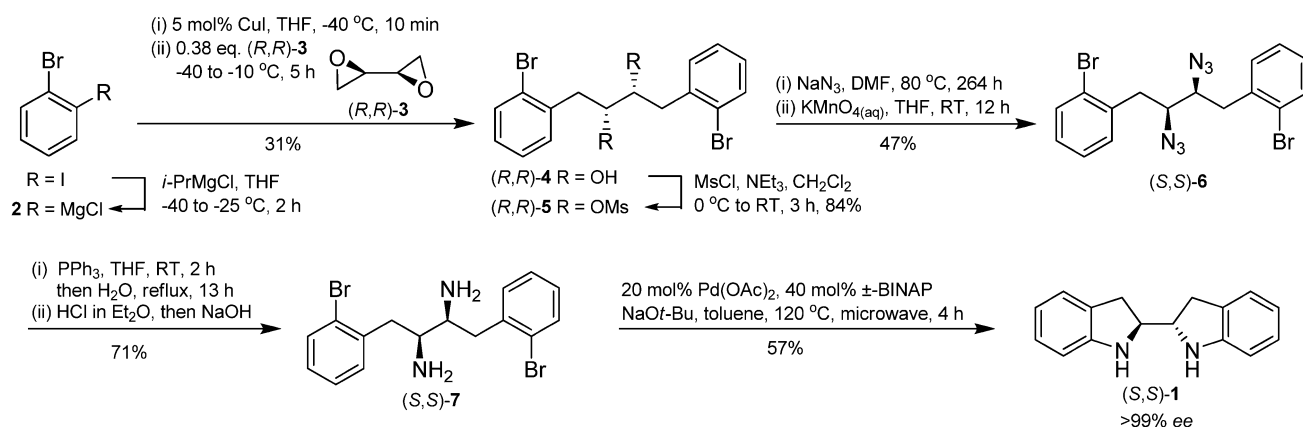
The biaziridine (*S,S*)-**8** has been prepared previously from D-tartaric acid using two cyclisation strategies – a Staudinger reduction and a traditional S_N2 substitution.⁹ In our hands, only the S_N2 cyclisation sequence provided the biaziridine in high yield – initial attempts to prepare the product using the alternative Staudinger approach resulted in poor yields.

The CuBr·SMe₂ catalysed¹³ ring opening of the biaziridine (*S,S*)-**8** with Grignard **2** gave the expected dicarbamate

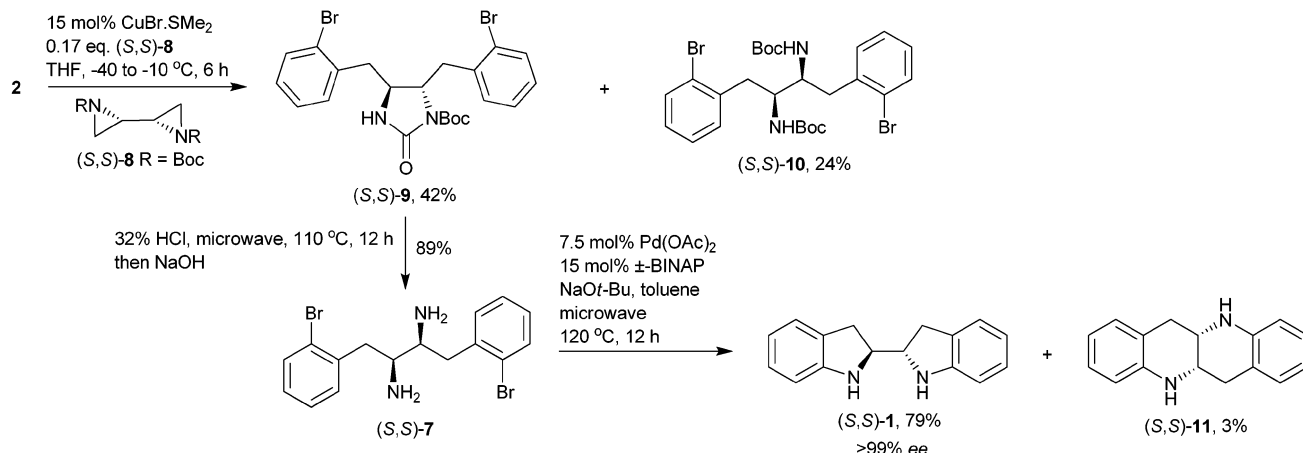
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† Electronic supplementary information (ESI) available: Synthetic procedures, X-ray data, NMR spectra and HPLC traces of 2,2'-biindoline structures. CCDC [794927–794928]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc04045b



Scheme 1 The synthesis of enantiopure 2,2'-biindoline structure **1** starting from chiral 2,2'-bioxirane.



Scheme 2 The synthesis of enantiopure 2,2'-biindoline structure **1** starting from chiral 2,2'-biaziridine.

(S,S)-10 (24%), however the major product was the imidazolidinone (S,S)-9 (42%) arising from intramolecular nucleophilic attack of the intermediate nitrogen anion on the adjacent Boc group.

Although this outcome was unforeseen, the formation of the imidazolidinone would not be detrimental to the intended synthesis providing hydrolysis to the diamine could be affected. In the event, the *N*-Boc substituent was easily removed but the urea unit proved highly resilient and was only cleaved under the most forcing conditions¹⁴ – prolonged heating with conc. HCl under microwave irradiation. Thus under these conditions the imidazolidinone (S,S)-9 was able to be hydrolysed to the diamine (S,S)-7 in high yield (89%). Upon attempting a larger scale HCl microwave hydrolysis however, the diamine was obtained in a mixture with the Boc-deprotected imidazolidinone (not illustrated). The incompleteness of this reaction was a direct result of solubility problems brought about by the need to significantly increase the substrate concentration to satisfy the volume limitations of our microwave vessel – larger scale synthesis would be easily achieved with the use of a larger microwave vessel.¹⁵

The final cyclisation¹⁶ was carried out, optimising the conditions described in Scheme 1, to afford the desired biindoline (S,S)-1 in good yield (79%, >99% ee)¹⁷ in addition to a small quantity of the novel naphthyridine isomer (S,S)-11 (3%) formed *via* the alternative cyclisation pathway.¹⁸

The structure of the biindoline was unequivocally confirmed by X-ray analysis of crystals grown from CH₂Cl₂/MeOH (Fig. 1A) in which it can be observed that the free ligand

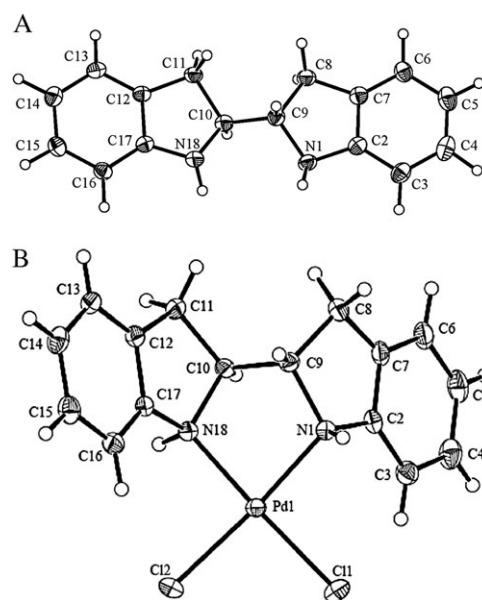


Fig. 1 X-Ray analysis of the free 2,2'-biindoline (A) and its complex with Pd(II) (B), the latter confirming the absolute stereochemistry and illustrating the helical nature of the ligand–Pd complex.

adopts an essentially flat conformation, where H9 is staggered with H10.

The palladium(II) dichloride complex of the biindoline was also prepared by the addition of $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ to a solution of the ligand in CH_2Cl_2 . The complex precipitated immediately as a yellow/orange powder (95%) that was sparingly soluble in all solvents. X-Ray analysis of crystals grown from acetonitrile confirmed the absolute stereochemistry of the complex, and demonstrated the desired helical conformation of the ligand around the palladium atom (Fig. 1B).

In summary, we have performed the first two syntheses of enantiopure 2,2'-biindoline using bioxirane **3** and biaziridine **8** as the chiral precursors, both of which were easily prepared from tartaric acid. The key step of both routes was the copper(I) catalysed ring opening of each precursor with Grignard **2**, providing alternate pathways to the diamine (S,S)-**7** which was regioselectively cyclised to (2S,2'S)-2,2'-biindoline.¹⁹ In a comparison of the two strategies, the biaziridine enabled a shorter and more efficient synthesis of the target compound. However, in order to circumvent the formation of undesired side products in the key ring opening step and thus avoid complications in subsequent hydrolysis to the penultimate diamine, we are currently investigating the use of a different N-protecting group for the sequence. Extension of the bioxirane and biaziridine as building blocks for a range of further chiral diamine ligands is also under investigation.

Notes and references

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- A small quantity of the Staudinger PPh_3O by-product remained after this purification process.
- Evidence of a trace quantity of the alternative isomer naphthyridine (S,S)-**11** (see Scheme 2) was provided by TLC analysis but no attempt was made to isolate the product in this case.
- Conditions for the preparation of the diBoc derivative: Boc_2O , NEt_3 , THF, RT, 144 h, 76%.
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- HCl (2 M) in AcOH at reflux, $\text{Ba}(\text{OH})_2$ in 80% EtOH at reflux and conc. HCl/MeOH (8 : 1) at reflux were all found to remove the N-Boc substituent but were ineffective in cleavage of the urea.
- The dicarbamate (S,S)-**10** was also converted into the diamine (S,S)-**7** using typical conditions of TFA at RT in a 66% unoptimised yield.
- The cyclisation reaction was performed using the mixture obtained from the larger scale (incomplete) hydrolysis which contained the diamine (S,S)-**7** and the Boc-protected imidazolidinone. The yields given are based on the initial quantity of (S,S)-**7** present. The latter compound was inert to the cyclisation conditions.
- The enantiomeric purity was determined in the same fashion as that for the product synthesised from bioxirane (R,R)-**3**.
- Naphthyridine (S,S)-**11** is structurally related to the commercially available chiral diamine ligand (4aS,8aS)-decahydro-1,5-naphthyridine, which is used in copper catalysed enantioselective aryl homo-coupling reactions. Therefore, it is of interest to us to investigate a method to reverse the regioselectivity of the cyclisation in order to obtain larger quantities of naphthyridine (S,S)-**11** for its testing as a new chiral ligand.
- The corresponding (R,R)-biindoline would be accessible in the same fashion from the bioxirane and biaziridine precursors derived from L-tartaric acid.