SHORT COMMUNICATION

EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201501058

A Modular Synthesis of Multidentate S-, N- and O-Containing Meta- and Paracyclophanes

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Keywords: Macrocycles / Aziridine / Dithiol / Chiral pool / Metacyclophanes

The development of a modular approach to macrocycle assembly has enabled the synthesis of a library of pyridine-based macrocycles possessing multiple donor sites where chirality was readily introduced from (*R*)- or (*S*)-alanine, a representative amino acid. The facile, regioselective, nucleophilic ring opening of aziridines by dithiols enabled the synthesis of thioether-based linkers which on subsequent alkylation provided access to optically pure macrocycles.

Introduction

Transition metals are not only vital to life (iron, copper, zinc) but can also display accumulative and acute toxicity (cadmium, mercury).[1] In general, the facility to detect, selectively remove or attenuate the chemistry/biochemistry of heavy metals has many potential applications ranging from water treatment to the management of life-changing disease states.[2] It is now apparent that mixed-donor macrocyclic ligands, which incorporate both "soft" and "hard" donor sets, can offer a range of co-ordination modes[3] (either *exo*- or *endo*-) that are not available to ligand systems that possess only "hard" donor sites. The ability of thioether based ligands to bind to metals has therefore taken on an extra dimension leading to ligands that are capable of binding to "soft" metal centres.[4]

The use of aziridines as chiral pool starting materials is now well established[5] and the aziridine moiety is also a key structural motif present in a number of natural products.[6] Key to the use of aziridines in synthesis is their accessibility, in optically pure form,[7] coupled with their ability to undergo regioselective ring opening with a range of nucleophiles in a regio- and stereo-defined manner.[8] In this work we present our findings on the use of aziridines as chiral pool materials in the synthesis of macrocycles bearing both soft and hard donor centres.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201501058.

Results and Discussion

Previously Bailey et al. had reported the synthesis of a range of pyridine-derived macrocycles with the aim of evaluating their efficiency in a number of catalytic, asymmetric processes.[9a] In the pursuance of this goal the synthesis of ester **1** and ether **2** was also attempted. While the synthesis of diester **1** was accomplished this system proved to be hydrolytically unstable;[9b] the synthesis of ether **2** was also marred by the apparent lack of regio control exhibited during the ring opening of aziridine (*S*)-**3** with oxygen-centred nucleophiles such as **4** (Figure 1).[8g]

At this point the focus of our investigation switched to the reaction between aziridine **3** with sulfur nucleophiles. These reactions are known to proceed under milder conditions than those of their oxygen counter parts.[8h,8j] Ultimately, we wished to probe whether a two-directional, aziridine ring opening – toluenesulfonamide cyclisation strategy, could be utilised in the synthesis of macrocycles possessing a variety of donor centres (Figure 2).

We were aware of only a limited number of reports concerning the use of dithiols in the crucial aziridine ring-opening reaction,[10] a reaction that we wished to address in the initial phase of this investigation. Encouragingly we noted, in a trial experiment, that reaction between (*S*)-**3** and thiol **7** (1.0 equiv.) in methanolic triethylamine[11] (2.1 equiv.; 35 °C, 4.5 h) afforded the toluenesulfonamide **8** in 86% yield after chromatography (Scheme 1; see the Supporting Information for details).

Analysis of the ^{1}H NMR spectrum of the crude reaction mixture leading to **8** indicated that the reaction was completely regioselective, with attack of the thiol taking place at the least encumbered, methylene, carbon of (*S*)-**3**. Conducting this reaction in a focused microwave reactor,[12] but under otherwise identical conditions, had no observable effect on either the yield or rate of the reaction. The general-

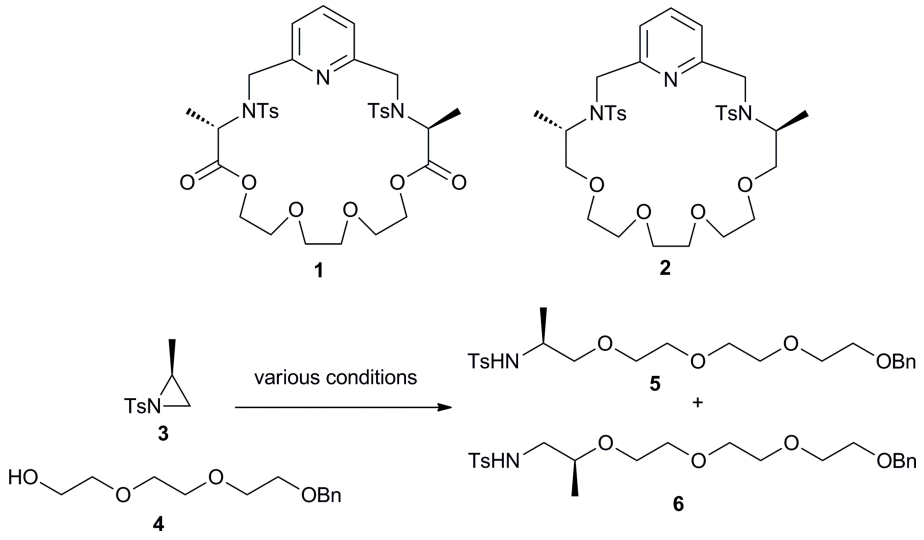


Figure 1. Previous studies by Bailey et al.[9]

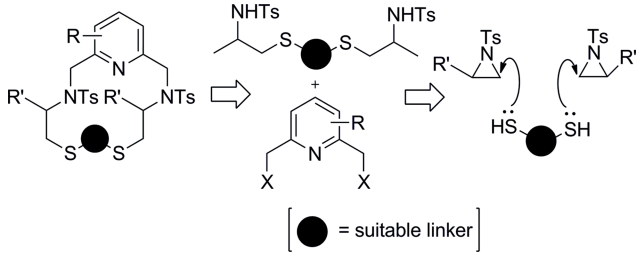
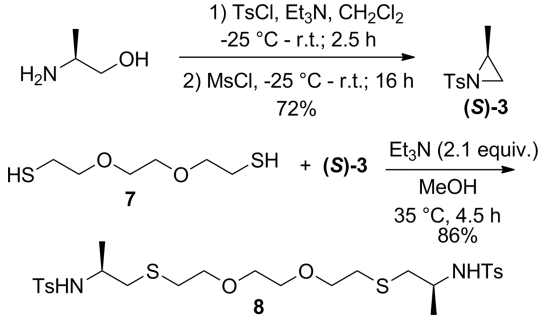


Figure 2. Two-directional aziridine ring opening – toluenesulfonamide cyclisation reactions.



Scheme 1. Two-directional aziridine ring-opening reaction.

ity of this protocol was next evaluated by using a series of commercially available dithiols in combination with either (*S*)-**3** or (*R*)-**3**. In all cases the alkylation reactions were highly regioselective and afforded the desired bis-alkylated products in good isolated yields, Figure 3.

The structure of the bis-toluenesulfonamide **10** was also confirmed unambiguously by way of a single-crystal X-ray structure determination (see Supporting Information for details).[13]

Extension of this basic strategy to heterocyclic thiols was also briefly investigated. Hence, reaction of bismuthiol (pK_{a1}1.4; pK_{a2} 7.4),[14a] a reagent commonly employed in trace metal analysis,[14b,14c] with (*S*)-**3** in the presence of methanolic triethylamine, as above, afforded **11** in 82% yield. The use of (*R*)-**3** in these reactions also proceeded smoothly enabling the isolation of **12** in good overall yield (61%). The regiochemistry of these double alkylation reactions (S vs. N of the thiadiazole ring) was evident from their ^{13}C NMR spectra on the grounds of symmetry and chemical shift [C(2)–S/C(5)–S at δ = 165.59 ppm].[14d,14e]

The synthesis of the more rigid linker, **15**, was also accomplished via the intermediacy of dithiol **14**. Reaction of 1,3-bis(bromomethyl)benzene **13** with thiourea (2 equiv.; EtOH; 3 h) followed by hydrolysis of the of thiouronium salt (NaOH, aq.; 4 h) afforded the dithiol **14** in a quantita-

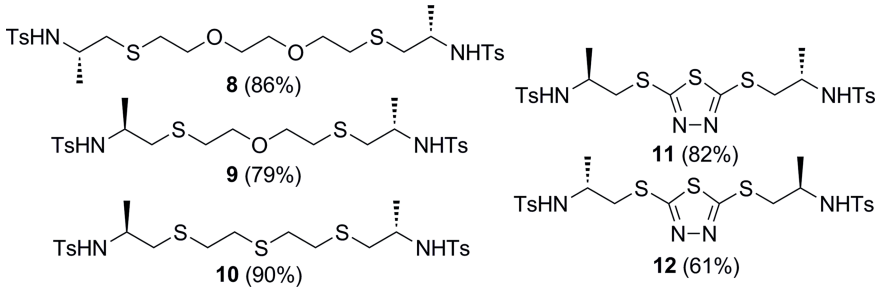
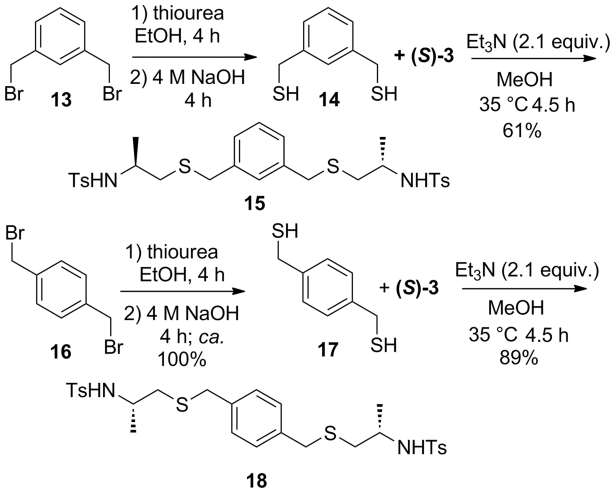


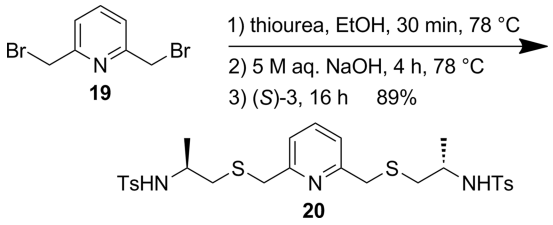
Figure 3. Generality of aziridine ring-opening reaction with dithiols.

tive yield (Scheme 2) after acidification.[15] Reaction of dithiol **14** with aziridine (*S*)-**3** in methanolic triethylamine (2.1 equiv.) afforded **15**, a colourless, crystalline solid, in 61% yield. This sequence was also repeated with 1,4-bis-(bromomethyl)benzene **16** and resulted in the isolation of bis-toluenesulfonamide **18** in 89% yield over the three steps.



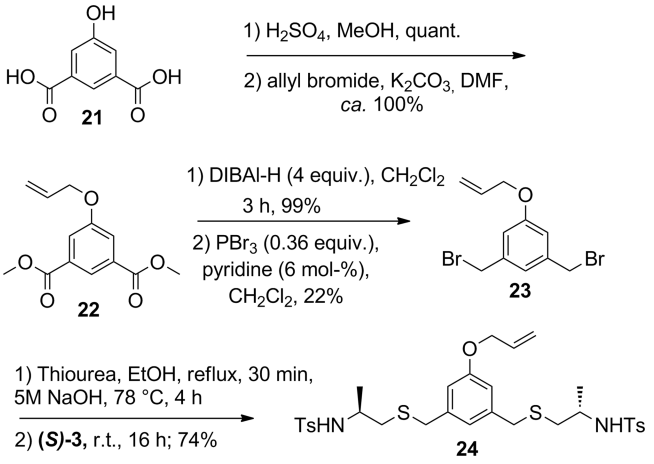
Scheme 2. Synthesis of more rigid, benzylic, linkers.

Given the malodorous nature of many of these thiols we also demonstrated the feasibility of undertaking a one-pot, three-step procedure for the preparation the bis-toluenesulfonamide **20**. Hence, conversion of 2,6-bis(bromomethyl)pyridine **19**, which is readily available from dipicolinic acid, to its bis-thiouronium salt (thiourea, 2 equiv.; EtOH, 78 °C; 30 min), followed by thiolate liberation (NaOH aq., EtOH, 78 °C) and addition of (*S*)-**3** afforded the bis-toluenesulfonamide **20** in 89% overall yield after chromatography (Scheme 3).[16]



Scheme 3. Synthesis of a pyridine-containing linker.

In wishing to incorporate additional functionality into the final macrocycle the synthesis of bis-toluenesulfonamide **24** was also investigated. Conversion of 5-hydroxyisophthalic acid **21**, into the allylated diester **22** was readily accomplished in essentially quantitative yield using standard methodology (see Supporting Information for details). Reduction of **22** (DIBAL-H, 4 equiv.; CH_2Cl_2) to the diol and conversion to the known dibromide **23**[17] (PBr_3, 0.3 equiv.; pyridine, 6 mol-%; 22% yield) followed by the implementation of our in situ thiol generation/alkylation reaction afforded bis-toluenesulfonamide **24** in 74% yield (Scheme 4).



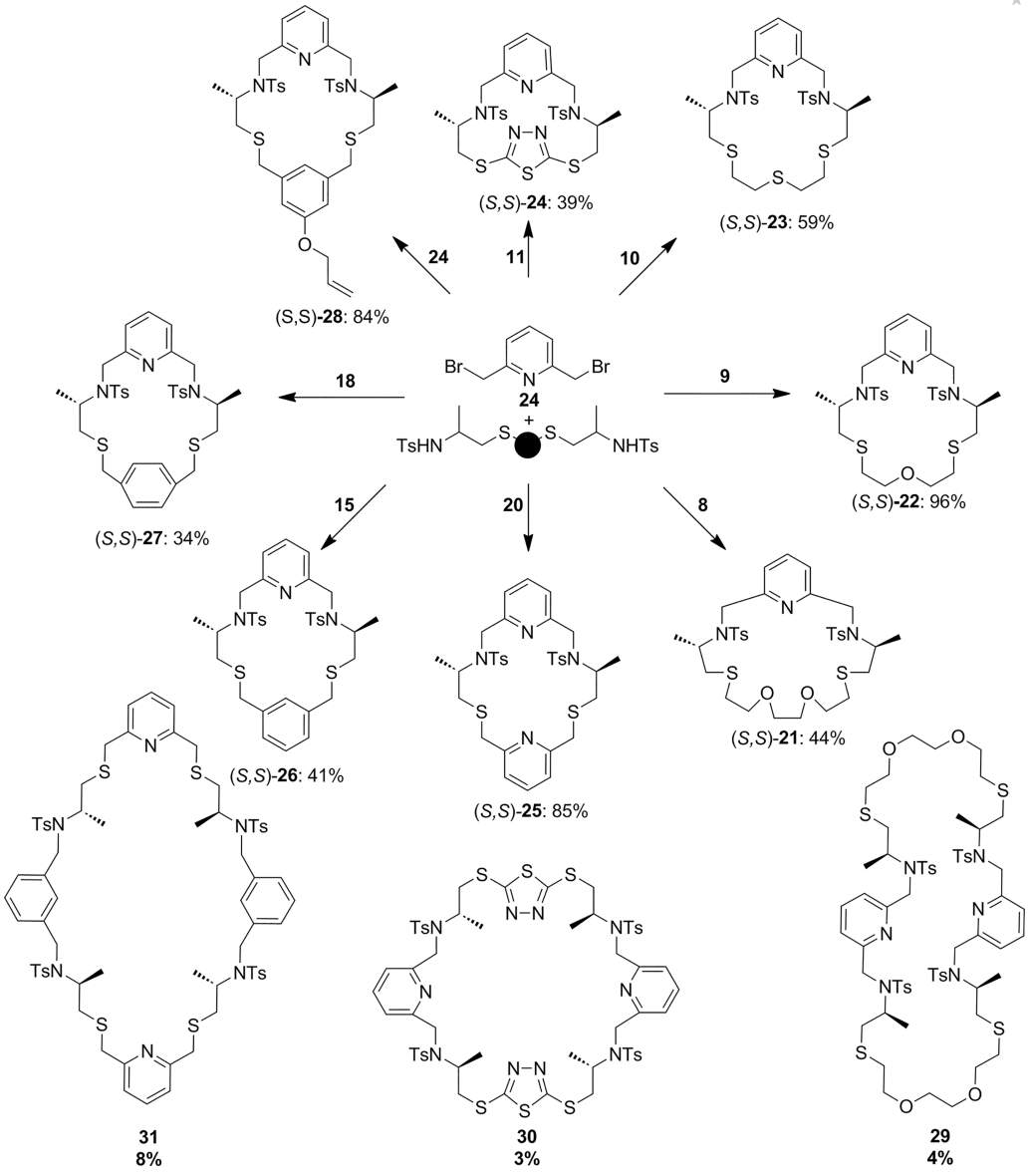
Scheme 4. Synthesis of functionalized linkers.

Having successfully prepared a small library of linkers (**8**, **9**–**12**, **15**, **18**, **20** and **24**), their incorporation into a macrocyclic framework was next investigated. Macrocyclisation[18] of these linkers with dibromide **19** was routinely conducted in DMF as the solvent (typically at 3 mM concentrations) with Cs_2CO_3 (5 equiv.) as the base and afforded a series of *meta*- and *para*-cyclophanes in yields ranging from 39–96% (Scheme 5). In certain cases minor quantities (3–8%) of "expanded" macrocycles[19] (such as **33**–**35**) were also isolated from the macrocyclisation reaction although in these cases purification of the major component was readily achieved by column chromatography. We were also fortunate to grow crystals of (*S*,*S*)-**26** and (*S*,*S*)-**28** which proved suitable for X-ray crystallographic analysis.

Although these two compounds are closely related, analysis of their crystal structures revealed a number of conformational subtleties in the solid state. In (*S*,*S*)-**26** the macrocyclic core adopts a conformation in which both the linker aromatic and pyridine rings are *syn*-disposed, generating a "Pacman"[20] structure in which the link between S1 to S2 takes up a "boat–chair" arrangement,[21] both S1 and S2 are *exo*-disposed. There is a noticeable tilt of the pyridine ring towards the aromatic ring in the linker (angle between the mean planes of each ring = 40.2°) and a relatively short H26B–C33 separation of 2.98(4) Å, which may be indicative of π–π and CH–π interactions, respectively.[22] Finally, the C19–N1–C1–C2 and C13–N2–C12–C11 torsion angles in **26** [75.8(2)° and 78.23°, respectively] are such that the C27/C28 methyl groups adopt a pseudo *trans*-diaxial disposition with respect to the macrocyclic core [C27–C1–C2–S1 = –72.6(9)°; C28–C12–C11–S2 = –161.4(5)°] resulting in a large C27–C28 separation of 8.0(4) Å (Figure 4).

In comparison to (*S*,*S*)-**26**, the X-ray structure of (*S*,*S*)-**28** proves to be much more complex in that this macrocycle adopts three crystallographically distinct conformations in the solid state.[22]

Two limiting conformations for this structure are depicted in Figure 5. Not unexpectedly, there is considerable



Scheme 5. Exemplification of the macrocylisation step. Reagents and conditions: **19** (1 equiv.), Cs_2CO_3 (5 equiv.); spacer **8**, **9**, **10**, **11**, **15**, **18**, **20 or 24**, (1 equiv.), DMF (300 mL $mmol^{-1}$ dithiol); 20 °C, 24 h.

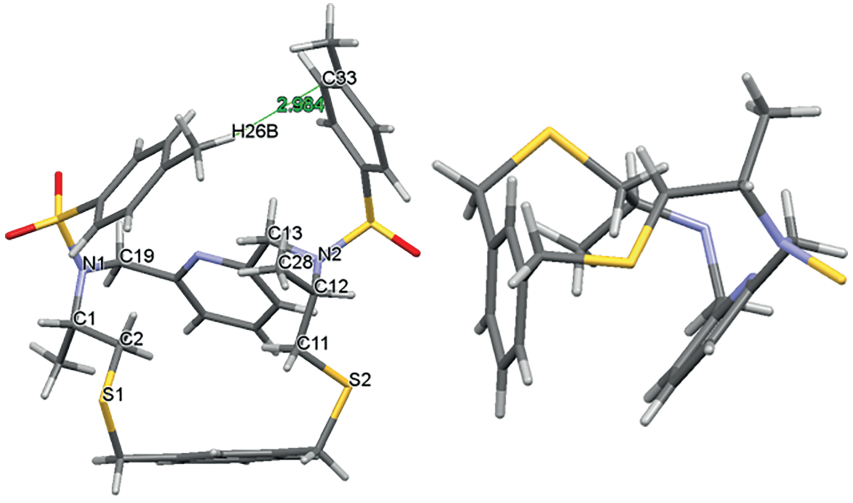


Figure 4. X-ray structure of (*S*,*S*)-**26** (hydrogen atoms omitted for clarity).

disorder about the allyloxy group in both (*S*,*S*)-**28a** and (*S*,*S*)-**28b**. Both of these structures exhibit the "Pacman" motif about the macrocyclic core, as observed for (*S*,*S*)-**26**, and, once again, the pyridine and aromatic linker residues are tilted towards one another.

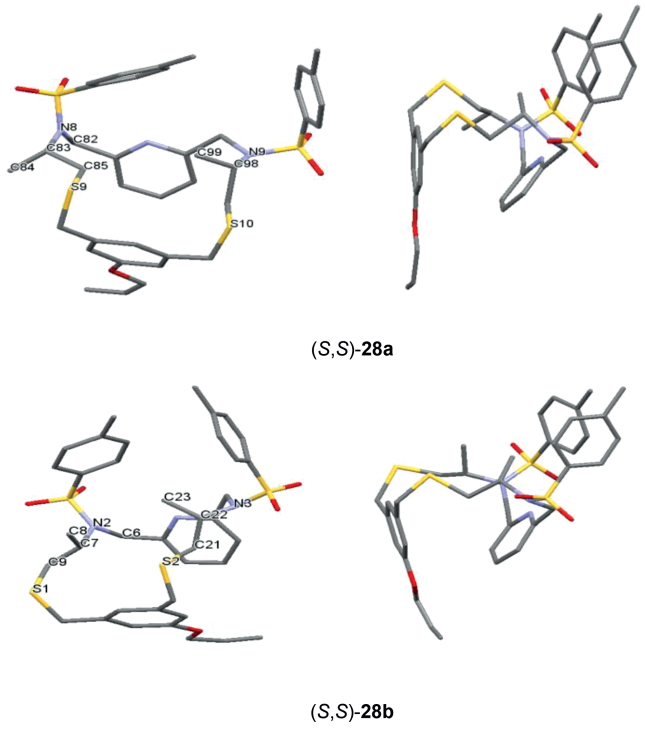
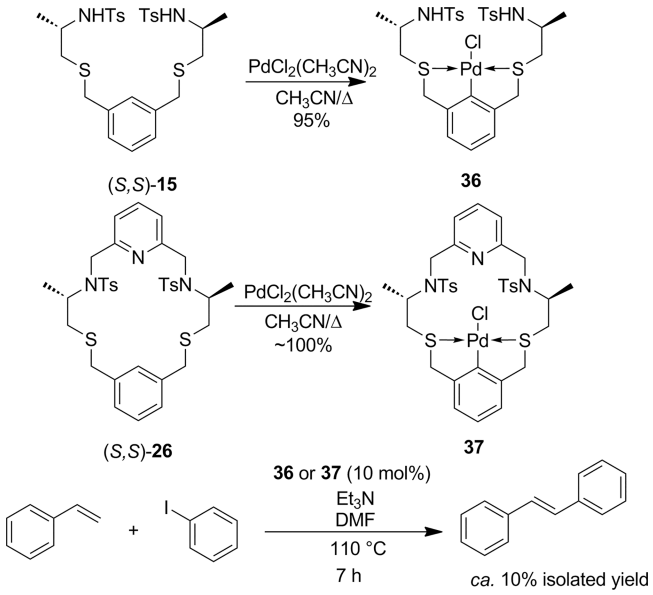


Figure 5. X-ray structure of (*S*,*S*)-**28a** and (*S*,*S*)-**28b** (hydrogen atoms omitted for clarity).

In both (*S*,*S*)-**28a** and (*S*,*S*)-**28b** the ring sulfur atoms are *exo*-disposed, but in both of these cases the linker, S9 to S10 and S1 to S2, adopt a boat–boat conformation. Rotation about C83–C85 in (*S*,*S*)-**28a** generates (*S*,*S*)-**28b** with a concomitant conformational change within the macrocycle such that the methyl groups associated with the core now point towards each other [(*S*,*S*)-**28a**: C84–C99 = 6.6(2) Å; (*S*,*S*)-**28b**: C8–C23 = 3.8(6) Å]. While C85 was inward-pointing in (*S*,*S*)-**28a** [C82–N8–C83–C85 = 71.5(1)°] C9, the analogous atom in **28b**, points to the outside of the macrocyclic ring [C6–N2–C7–C9 = –82.9(2)°]. In solution, the well-resolved ^{1}H NMR spectrum of (*S*,*S*)-**28** in $CDCl_3$ at 25 °C is indicative of a rapid interchange[23] between conformational isomers at ambient temperatures.

With the synthesis of substrates such as **15** and **26** at hand we initiated a study into their metalation chemistry. Initial studies showed that palladation of both **15** and **26** was relatively facile [$PdCl_2(CH_3CN)_2$; CH_3CN, reflux; 24 h] and afforded the S,C,S-pincer complexes **36** and **37** in essentially quantitative yield.[24] Both of the pincer complexes served as catalysts[25] in a trial Heck reaction between iodobenzene and styrene, affording *trans*-stilbene (ca. 10% isolated yield after 7 h), although at a slower rate than with a "ligandless" source of palladium [$Pd(OAc)_2$, Et_3N, DMF, 100 °C, 7 h; 91%] (Scheme 6).



Scheme 6. Synthesis of S,C,S-Pd pincer complexes.

Conclusions

In conclusion we have developed a modular approach to the synthesis of a family of conformationally mobile, mixed-donor, pyridine-based macrocycles which involves the two-directional capping of dithiols with aziridines. The use of readily available chiral pool starting materials derived from either (*R*)- or (*S*)-alanine enables access to optically pure pyridine-containing macrocycles[26] the complexation phenomena of which are now under investigation.

Experimental Section

Supporting information: (see footnote on the first page of this article): Full experimental procedures and characterisation of all new compounds.

CCDC-1411546 (**10**), CCDC-1411542 (**26**) and CCDC-1411557 (**28**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

We thank the EPSRC (grant number EP/K039547/1) for the provision of Bruker NMR spectrometers and an Agilent SuperNova X-ray diffractometer. O. K. R. thanks the University of Manchester for a research studentship.

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Received: August 14, 2015
Published Online: October 8, 2015

