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[2.2]Paracyclophane derivatives in asymmetric catalysis

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1 Introduction

The use of asymmetric catalysts that do not rely exclusively on tetrahedral chirality is well documented. These catalysts incorporate ligands based on, for example, an axially chiral binaphthalene backbone,[1] a planar chiral ferrocene derivative,[2] or a planar chiral arene transition metal complex.[3] There are, however, relatively few examples in the literature of the use of planar chiral cyclophane based ligands in catalytic asymmetric processes, despite the fact that the parent [2.2]paracyclophane was first synthesised over half a century ago.[4] This is in part due to the nature of cyclophanes themselves, whose ease of resolution becomes increasingly difficult as the length of the bridging tether is increased.[5] Planar chiral derivatives of [2.2]paracyclophane, however, undergo racemisation only at relatively high temperatures, and their cyclophane backbone is chemically stable towards light, oxidation, acids and bases.[6,7]

This review sets out to highlight the growing importance of [2.2]paracyclophanes as planar chiral ligands by providing a comprehensive coverage of the applications of mono- and disubstituted [2.2]paracyclophane derivatives in asymmetric catalysis. It may be argued that the limiting factor in this area of chemistry is the shortage of attractive synthetic routes to enantiopure [2.2]paracyclophanes. For this reason, each section of the review is supplemented by a description of typical approaches used to access the class of cyclophane under discussion. First of all, however, it is perhaps appropriate to define the stereochemical notation that is generally adopted for [2.2]paracyclophanes.

2 Stereochemical notation

The assignment of R_p and S_p for planar chiral [2.2]paracyclophanes[8] is initiated by choosing a plane that contains as many of the atoms of the molecule as is possible and that arises by the desymmetrisation of a plane of symmetry. So for the monosubstituted paracyclophanes depicted in Fig. 1, the more highly substituted benzene ring (the bottom one as drawn in Fig. 1) is considered the chiral plane. To find the descriptor, the chiral plane is viewed from the out-of-plane atom closest to the plane (if there are two or more candidates, the one closest to the atom of higher priority is chosen according to the Cahn–Ingold–Prelog (CIP) system of stereochemical assignment[8a,8b]). This "pilot" atom is marked with an arrow and is assigned as carbon atom number one for the cyclophane nomenclature.[9] Then, if the three adjacent atoms a, b, c (again chosen by CIP precedence if there is a choice) describe a clockwise array in the chiral plane, when viewed from the "pilot" atom, the descriptor is R_p, and if the array is counterclockwise, the descriptor is S_p, where p denotes planar chirality. The carboxy[2.2]paracyclophane shown in Fig. 1, is thus S_p. Once the "pilot" atom

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Jamie D. Knight

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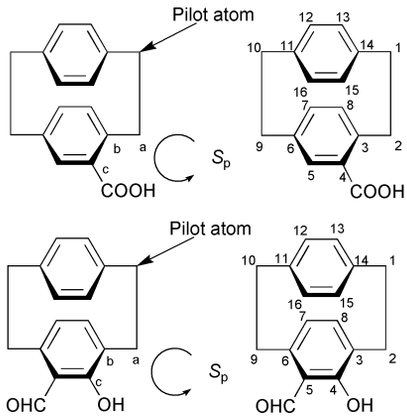


Fig. 1

has been identified, numbering continues in sequence towards the atom of highest priority according to the CIP system and then around the paracyclophane system. This cyclophane is thus (S_p)-4-carboxy[2.2]paracyclophane, and the disubstituted cyclophane depicted in Fig. 1 is (S_p)-5-formyl-4-hydroxy-[2.2]paracyclophane.

In the event that there are two identical chiral planes in a molecule, due to C_2 symmetry, clearly either plane may be chosen to identify the stereochemical descriptor (Fig. 2).

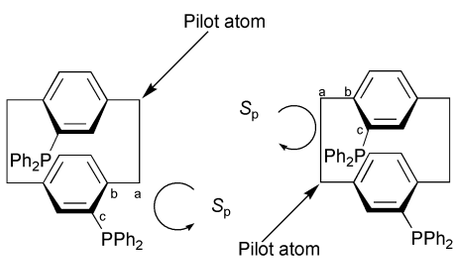


Fig. 2

Prelog and Helmchen[10] viewed planar chirality as a form of helicity. The sense of the helix is determined using the "pilot" atom and atoms a, b and c as specified above. It is apparent that R_p corresponds to a right handed helix, P, and S_p to a left handed helix, M. In practice either stereochemical assignment can be used and in certain instances the use of the helical descriptor can avoid ambiguity in the stereochemical classification of more complex paracyclophanes.[11] However, for the purpose of this review we will use the descriptors, R_p and S_p, to define the planar chirality present in the [2.2]paracyclophane derivatives discussed.

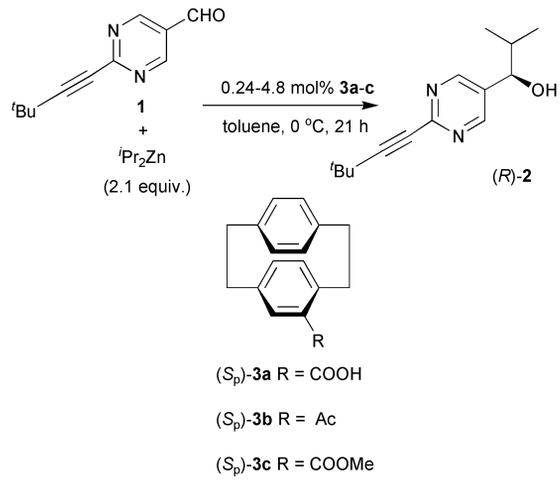
3 Monosubstituted [2.2]paracyclophanes

3.1 Applications in asymmetric catalysis

Planar chiral monosubstituted [2.2]paracyclophane derivatives have been employed in asymmetric diisopropylzinc additions to aldehydes, asymmetric cyclopropanation reactions and asymmetric epoxidation reactions. These pioneering studies have produced moderate to excellent enantioselectivities and yields.

Soai *et al.*[12a] examined the addition of diisopropylzinc to 2-(*tert*-butylethynylpyrimidine)-5-carbaldehyde **1** in the presence of ligands **3a**–**c** (Scheme 1).

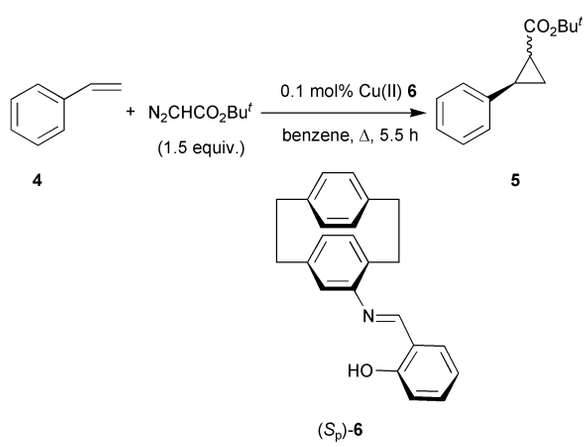
When (S_p)-(+)-4-carboxy[2.2]paracyclophane, **3a**, was used that had an enantiomeric excess of 99%, the product pyrimidyl alkanol (*R*)-**2** was obtained in 91% yield and 95% ee. The reaction was autocatalytic and using lower levels of optical purity of **3a** (29, 27 and 2.5% ee), still gave the product alkanol **2** in excellent enantiopurity (95, 91 and 89% respectively) and good yield (90–95%). Use of the acetyl cyclophane **3b** and the methoxycarbonyl cyclophane **3c** in the reaction also gave the alcohol



Scheme 1

2 in both high ee (92–95%) and yield (88–96%). In a recent continuation of the study of this reaction, monosubstituted hydrocarbon [2.2]paracyclophanes were found to be equally effective chiral initiators, affording product **2** in high yields and enantiomeric excesses.[12b]

Glatzhofer *et al.*[13] tested the Schiff-base *N*-salicylidene-4-amino[2.2]paracyclophane **6** in the copper(II) mediated cyclopropanation of a series of styrenes. The best enantiodifferentiation recorded for styrene (**4**) itself was obtained using *tert*-butyl diazoacetate which gave 41% ee for the *trans* isomer of **5** (82% conversion) and 13% ee for its *cis* isomer (14% conversion) (Scheme 2).



Scheme 2

It was concluded that the [2.2]paracyclophane catalyst could adopt a large number of conformations and this limited its ability to transfer chiral information to the substrate. A second generation of Schiff-base ligand that incorporated *tert*-butyl groups at the *ortho* and *para* positions of the phenol was thus developed (**7**, Fig. 3).[14] It was envisaged that the additional steric

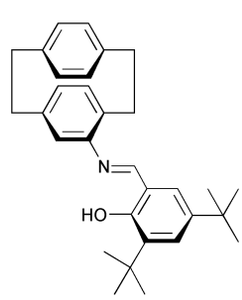
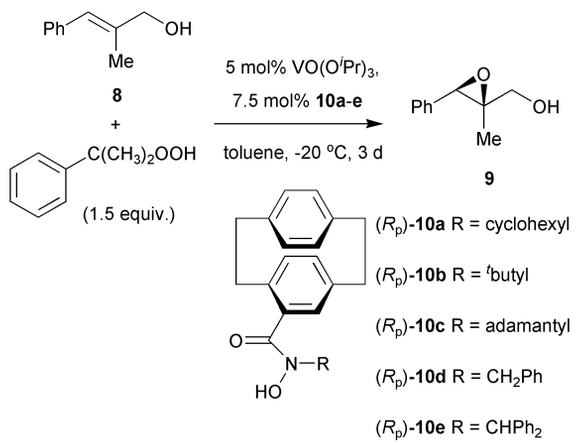


Fig. 3

bulk around the metal centre would present a more effective "chiral pocket". Improved enantioselectivities were indeed observed for styrene compared to ligand **6**, typified by the generation of the *trans* isomer of **5** in 68% ee (55% conversion) and its *cis* isomer in 54% ee (16% conversion).

Bolm and Kühn[15] have developed an interesting class of vanadium complexes based on *N*-hydroxy[2.2]paracyclophane-4-carboxylic amides **10** and used them as catalysts for the asymmetric epoxidation of allylic alcohols. Ligands **10a**–**e** were screened to identify the optimum ligand system for substrate **8** under the conditions depicted in Scheme 3. Cyclophane **10c**, where R = adamantyl, produced epoxide **9** in the best ee (52%) and in a yield of 88%.



Scheme 3

Several reaction parameters were then examined using ligand **10c** and substrate **8**. *tert*-Butyl hydroperoxide (5.5 M in decane) was identified as the most effective cooxidant giving an enantioselectivity of 71% in 85% yield, and it was discovered that a relatively low ratio of ligand to $VO(O^iPr)_3$ was required to effect a reasonable enantiomeric excess (1.5 or even 1.0). This was in contrast to the findings of Sharpless[16] and Yamamoto,[17] who found that with their systems it was necessary to use at least a three-fold excess of chiral ligand to avoid the presence of achiral $VO(O^iPr)_3$ that would catalyse the reaction in a racemic fashion.[18] Five further allylic alcohols were examined at the end of the study using ligand **10c** and *tert*-butyl hydroperoxide. These provided epoxides in good yield (73–89%) but moderate ee (38–71%).

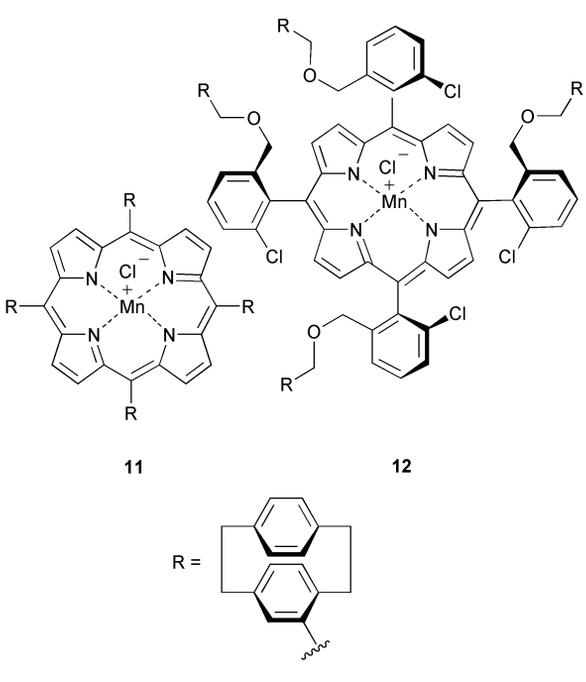


Fig. 4

Quici *et al.*[19,20] have synthesised a Mn(III)-*meso*-tetrakis-[2.2]paracyclophane-porpyhrin, **11**, and an atropisomerically pure (α,β,α,β)-tetraarylporphyrin **12** (Fig. 4) as novel catalyst systems for the enantioselective epoxidation of prochiral alkenes using NaOCl as oxidant.

Moderate enantioselectivities were obtained for conjugated olefins using **11** (22–31%), whilst poor levels of enantiopurity (<5%) were achieved with catalyst **12**. Nevertheless, the [2.2]paracyclophane substituted systems gave high turnover numbers comparable with those reported in the literature for analogous porphyrin-based systems.[21–24]

3.2 Synthetic approaches to enantioenriched ligands

The transition metal catalysts discussed in Section 3.1 contain ligands derived from a handful of non-racemic planar chiral monosubstituted [2.2]paracyclophanes. This section of the review summarises some of the best methods available for the synthesis of several key enantiomerically enriched monosubstituted [2.2]paracyclophane derivatives. At present this area is dominated by classical resolution procedures.

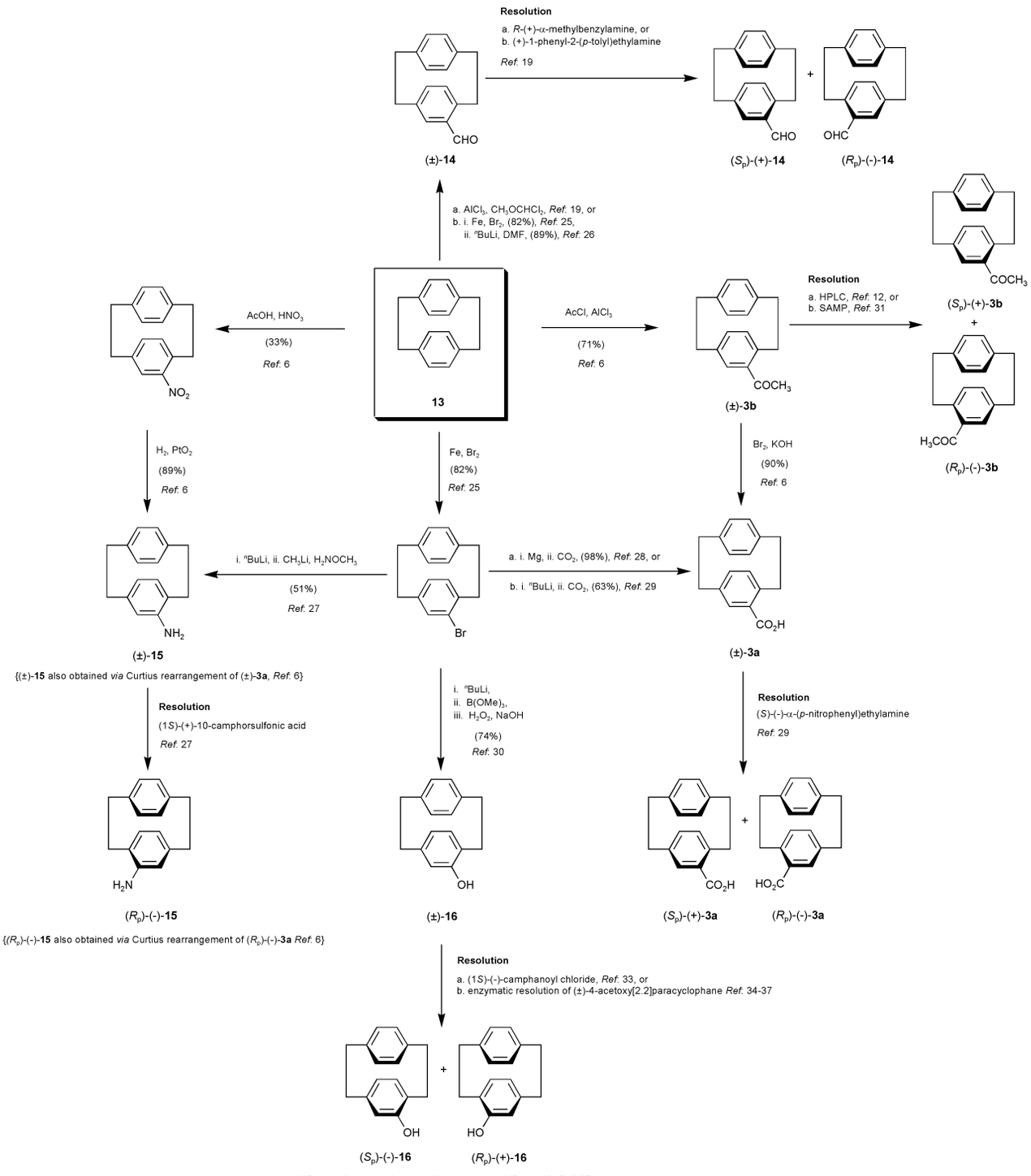
Commercially available [2.2]paracyclophane **13** has been converted into racemic 4-carbaldehyde[2.2]paracyclophane **14**,[19,25,26] 4-acetyl[2.2]paracyclophane **3b**,[6] 4-amino[2.2]paracyclophane **15**,[6,25,27] 4-carboxy[2.2]paracyclophane **3a**,[6,25,28,29] and 4-hydroxy[2.2]paracyclophane **16**,[25,30] by standard synthetic reactions (Scheme 4). These derivatives have subsequently been resolved as described below.

One of the best approaches to the enantioenriched aldehyde (S_p)-(+)-**14** has been developed by Quici *et al.* and involves diastereoisomeric imine formation between (±)-**14** and (*R*)-(+)-α-methylbenzylamine.[19] A single crystallisation of the crude product afforded crystals enriched in the (R,S_p) diastereoisomer. A further crystallisation of this material afforded the (R,S_p) diastereoisomer in ≥98% de. Hydrolysis on silica gel during column chromatography gave (S_p)-(+)-**14** in ≥98% ee and in 20% isolated yield.† The enantiomer, (R_p)-(−)-**14**, was not isolated during this procedure, but instead was obtained by diastereoisomeric imine formation between (±)-**14** and (+)-1-phenyl-2-(*p*-tolyl)ethylamine.[19] Repeated crystallisation of the imine followed by hydrolysis afforded (R_p)-(−)-**14** in ≥98% ee and 26% isolated yield. The enantiomeric purity of (S_p)-(+)-**14** was determined by reduction to the corresponding alcohol and formation of its Mosher's ester.

Enantiomerically pure samples of the acetyl derivative **3b** have been obtained from the resolution of (±)-**3b** by HPLC using a chiral stationary phase column.[12] Arguably one of the best routes devised to enantioenriched **3b**, however, involves diastereoisomeric imine formation with (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP).[31] Crystallisation of the 1 : 1 mixture of diastereoisomers formed between **3b** and SAMP from ethanol afforded a sample enriched in the less soluble (S,S_p) salt, and a further crystallisation of this material afforded the pure diastereoisomer. The (S,R_p) salt was obtained diastereoisomerically pure by evaporation of the mother liquor of the first crystallisation, followed by two consecutive crystallisations from ethanol. Enantiomerically pure (S_p)-(+)– and (R_p)-(−)-**3b** were synthesised in 15 and 31% yield, respectively, upon hydrolysis of the corresponding SAMP-hydrazones with oxalic acid.

One of the best routes to enantiomerically pure (R_p)-(−)-**15** involves the hydrolysis of the diastereoisomeric salts formed

† The yields reported in this section of the review are calculated on the basis that the maximum theoretical yield obtainable from the resolution of the racemate into its respective enantiomeric components is 50% for each enantiomer.



Scheme 4

between (±)-**15** and (1*S*)-(+)-10-camphorsulfonic acid.[27] The less soluble (1*S*,R_p) diastereoisomer crystallises from ethyl acetate and is hydrolysed with sodium hydroxide to afford enantiopure (R_p)-(−)-4-amino[2.2]paracyclophane **15** in 24% yield. (S_p)-(+)-4-Amino[2.2]paracyclophane **15** was not isolated. The enantiomeric purity and absolute configuration of (R_p)-(−)-**15** were established by comparing the value of its specific optical rotation with that of a sample of known absolute configuration.[32] The enantiomeric purity was confirmed by bromination of the diazonium salt of (R_p)-(−)-**15** by a Sandmeyer reaction to give (R_p)-(−)-4-bromo[2.2]paracyclophane that was shown to be enantiomerically pure by HPLC analysis.[27]

Rozenberg and Belokon have devised the optimum route to date to enantiopure samples of the carboxylic acid **3a**. It proceeds *via* the resolution of (±)-**3a** by diastereoisomeric salt formation with (*S*)-(−)-α-(*p*-nitrophenyl)ethylamine.[29] The less soluble (*S*,S_p) salt crystallised from chloroform at −5 °C and was hydrolysed with hydrochloric acid, to give enantiopure (S_p)-(+)-4-carboxy[2.2]paracyclophane **3a** in 32% yield. The (*S*,R_p) diastereoisomer was isolated from the material obtained from the mother liquor and was hydrolysed with hydrochloric acid, to afford (R_p)-(−)-**3a** with a lower level of optical purity of 84%. A sample of (R_p)-(−)-**3a** was therefore combined with (*R*)-(+)-α-(*p*-nitrophenyl)ethylamine to give the (*R*,R_p) diastereoisomer which crystallised from ethanol and was hydrolysed in a similar manner, to give enantiopure (R_p)-(−)-4-carboxy[2.2]paracyclophane **3a** in 24% yield.

Access to enantioenriched samples of the phenol **16** has been achieved by resolution of (±)-**16** *via* ester formation with (1*S*)-(−)-camphanoyl chloride.[33] An initial crystallisation from ethyl

acetate afforded the (1*S*,R_p) diastereoisomer with a de >95%. Crystallisation of the mother liquor afforded the (1*S*,S_p) diastereoisomer with a de >91%. The diastereoisomeric purity of the diastereoisomers was improved to ≥99% by a series of further crystallisations, and the stereochemistry of the diastereoisomers was determined by X-ray crystallography. Cleavage of the diastereoisomeric esters using lithium aluminium hydride afforded enantiopure (R_p)-(+)-**16** and (S_p)-(−)-**16** in 10–11% isolated yield and >99% ee.

It is of note that Cipiciani *et al*. have used *Candida cylindracea* lipase (CCL) to resolve racemic 4-acetoxy[2.2]paracyclophane.[34] At 40 °C, 50% conversion in water at pH 7.2 using CCL took 96 h and gave (R_p)-(+)-**16** in ≥98% ee (46% yield) and (S_p)-(+)-4-acetoxy[2.2]paracyclophane in ≥98% ee (43% yield). Pietzsch *et al*. have shown that *Candida rugosa* lipase (CRL) is also an effective enzyme for this kinetic resolution.[35,36] At room temperature, on a preparative scale, 53% conversion in diethyl ether at pH 7 using CRL, took 95 h and gave (R_p)-(+)-**16** in 90% enantiomeric excess and 51% yield, and (S_p)-(−)-4-acetoxy[2.2]paracyclophane in >99% ee and 44% yield. Cipicani *et al*. later examined propan-2-ol treated CCL on a preparative scale and found that at 50% conversion after 8 h in hexane at pH 6.2, (R_p)-(+)-**16** was obtained in 97% ee (45% yield) and (S_p)-(−)-4-acetoxy[2.2]paracyclophane in 96% ee (48% yield).[37]

4 [2.2]Paracyclophanes with two substituents on one ring

4.1 Applications in asymmetric catalysis

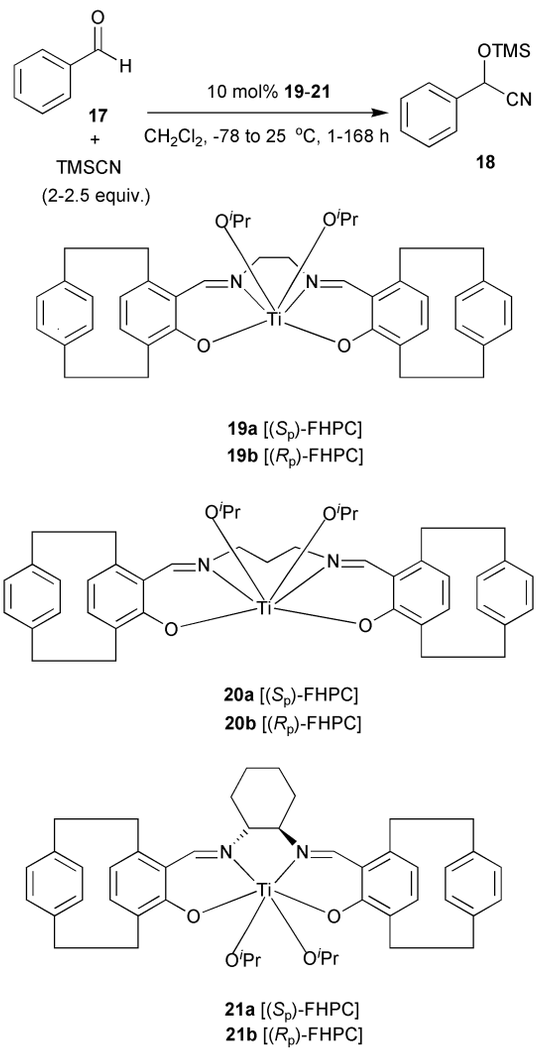
Disubstituted [2.2]paracyclophane ligands carrying substituents on the same aromatic ring have been employed in additions to aldehydes and imines, palladium catalysed allylic alkylation reactions, and oxidations of thioethers, giving good to excellent yields and selectivities.

Belokon *et al*. have synthesised a series of titanium(IV) salen complexes **19**–**21** utilising Schiff bases derived from (S_p)- and (R_p)-5-formyl-4-hydroxy[2.2]paracyclophane [(S_p)- and (R_p)-FHPC] for application in the asymmetric trimethylsilylcyanation of benzaldehyde **17** (Scheme 5).[38]

Use of 10 mol% of catalyst **19a** or **19b** and a ratio of TMSCN–benzaldehyde **17** of 2–2.5 at −78 °C for 120 h, gave the product **18** in 90% isolated yield and 82–84% enantiomeric excess. Raising the temperature of the reaction to 25 °C and reducing the reaction time to 4 h with **19a** gave (*R*)-**18** in a much lower enantiopurity of 22%. Exchange of the ethylenediamine backbone for a propylenediamine backbone gave catalysts **20**, which under similar experimental conditions resulted in either no conversion and/or racemic product **18**. Incorporation of additional chirality *via* the employment of (1*R*,2*R*)-diaminocyclohexane as the backbone in the titanium salen complexes, **21**, gave up to 90% isolated yield for the product **18**, but only moderate enantiomeric excesses of 17–49%.

Dahmen and Bräse have synthesised the [2.2]paracyclophane based ketimine ligands **24** and **25**, that possess both tetrahedral and planar chirality, and tested them in alkenylzinc additions to various aldehydes.[39] The alkenylzinc species was prepared *in situ* using a modification of Oppolzer's procedure: hydroboration of oct-1-yne **22** with dicyclohexylborane, followed by transmetalation with diethylzinc, gave the alkenylzinc species.[40] Subsequent addition of 2 mol% of **24a** or **24b** and benzaldehyde **17** at −10 °C furnished the chiral allyl alcohol product **23** in 64–70% yield and 68–81% ee, whilst the addition of 2 mol% of **25a** or **25b** gave **23** in 62–69% yield and 85–86% ee (Scheme 6).

It was found that (S,R_p)-**24a** and (S,R_p)-**25a** afforded the *S* stereoisomer of the product **23**, whilst (S,S_p)-**24b** and (S,S_p)-**25b** gave the *R* stereoisomer indicating that the stereochemical outcome of the reaction is dominated by the planar chirality. The scope of the asymmetric addition of alkenylzinc reagents



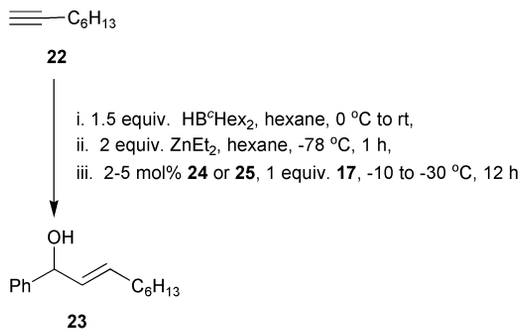
Scheme 5

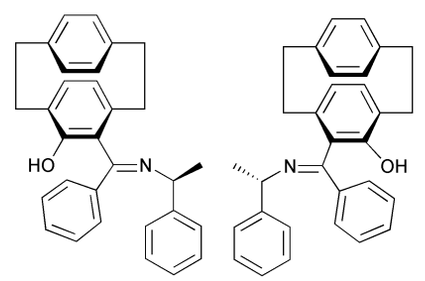
to aldehydes was then further investigated using (S,R_p)-**25a**. Changing the aldehyde to the electron deficient aldehyde, *p*-chlorobenzaldehyde, led to an improved enantioselection of 97% in 88% yield for the secondary alcohol product, whilst the use of an electron rich substrate, *p*-anisaldehyde, also gave a high enantiomeric excess of 91%, but in a lower isolated yield of 62%. Aliphatic and α-branched aliphatic aldehydes, problematic substrates for nearly all catalytic systems, gave optical purities of >98%. Next the effect of altering the alkyne substrate was examined. Changing the alkyne for hex-3-yne and the more sterically demanding *tert*-butylethyne gave lower enantiomeric excesses (64–75%) and isolated yields (78–86%) with benzaldehyde **17** and *p*-chlorobenzaldehyde. However, exchange of the transmetalating agent diethylzinc for dimethylzinc was shown to be beneficial, leading to selectivities of up to 89% for the reaction using *tert*-butylethyne and *p*-chlorobenzaldehyde.

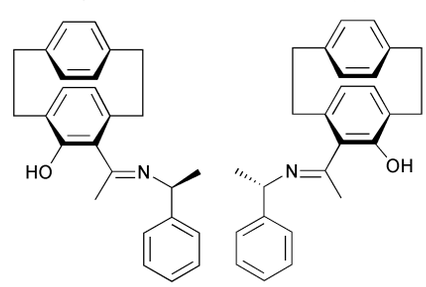
Belokon *et al*. have investigated the use of a novel titanium catalyst **27** in diethylzinc additions to benzaldehyde **17** (Scheme 7).[41]

The catalyst **27** was generated and used *in situ* according to methodology developed by Seebach.[42] Catalyst loadings of 0.15–0.25 equivalents were used and gave the *R* stereoisomer of the product ethylbenzyl alcohol **26** in moderate to excellent conversions (37–100%) and moderate enantioselectivities (22–36%).

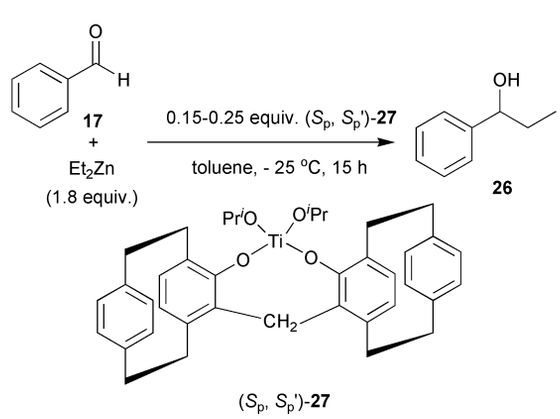
Dahmen and Bräse have used their novel *N*,*O*-planar chiral [2.2]paracyclophane ligands, **24** and **25**, in diethylzinc additions to various aromatic and aliphatic aldehydes.[43] The use of 1 mol% of **24a** with 1 equivalent of benzaldehyde **17** and 2







Scheme 6

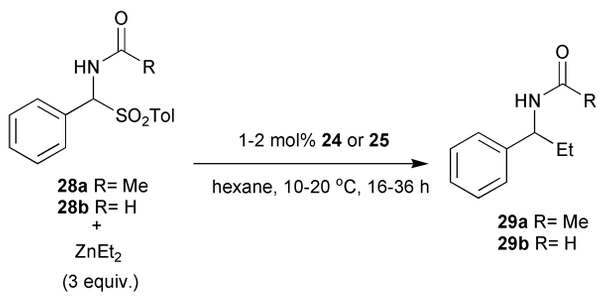


Scheme 7

equivalents of diethylzinc in toluene–hexane at 0 °C for 12 h, gave (*S*)-**26** in only 36% conversion and 60% ee. However, the use of diastereoisomer **24b** gave (*R*)-**26** in 100% yield and 85% ee. For **24b** almost all the selectivities were in the range 81–85% for the different aromatic substrates screened, whilst for **24a** either no conversion or low selectivities were observed. In contrast however, both diastereoisomers of **25** tested gave **26** in 94–100% yield and 82–83% ee under identical conditions. It was demonstrated that (S,R_p)-**24a** and (S,R_p)-**25a** afforded secondary alcohol products with *S* stereochemistry, whilst (S,S_p)-**24b** and (S,S_p)-**25b** gave the corresponding *R* stereoisomers, again indicating that the stereochemical outcome of the reaction was dominated by the planar chirality.

A recent review of diethylzinc additions to aldehydes, describing over six hundred ligand systems, revealed that only about a dozen ligands are capable of effectively catalysing diethylzinc additions to aliphatic and α-branched aliphatic aldehydes.[44] In this context it is of significant note that extremely high enantioselectivities were observed for the aliphatic and α-branched aliphatic substrates tested using ligands **24** and **25** (86–99%). Furthermore, ligands employed in diethylzinc additions are normally required in high loadings (10–15%) due to their tendency to form dimeric complexes; only a few ligands are reported to work on a 1–2% level. It is thus interesting that the ligands developed by Bräse can be used at levels as low as 0.5% without any apparent loss of selectivity. Even using ligand levels of 0.05% of **24b**, enantiomeric excesses of 91% were observed for cyclohexanecarbaldehyde and 80% for benzaldehyde with conversions of 75 and 92% respectively.

Dahmen and Bräse have further employed ligands **24** and **25** in diethylzinc additions to imines, starting from the precursors **28a** and **b** (Scheme 8).[45]



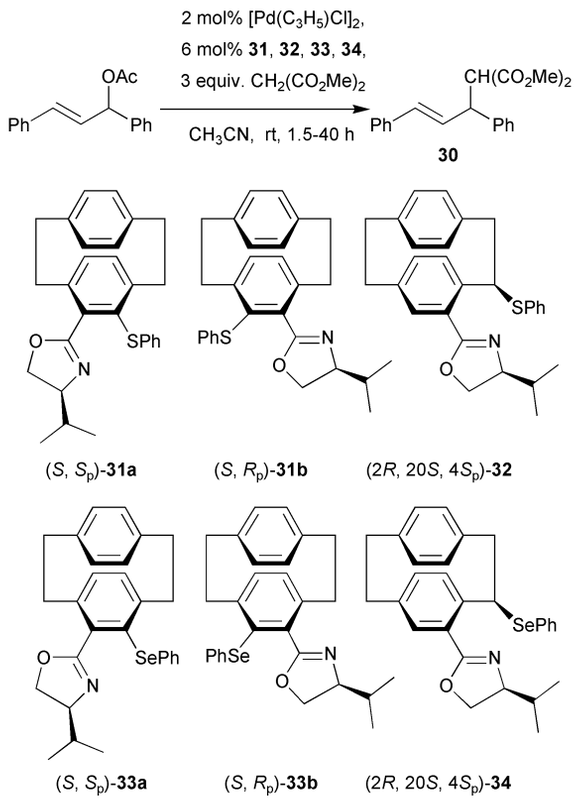
Scheme 8

The reaction with **28a** starts with the elimination of the sulfinate moiety and the formation of an *N*-acetyl imine; addition of diethylzinc in the presence of (S,R_p)-**25a**, afforded the amide (*R*)-**29a** in 50–92% yield and 63–80% enantiomeric excess. Use of ligands (S,R_p)-**25a** or (S,S_p)-**25b** in the diethylzinc additions to the *N*-formyl imine, **28b**, afforded **29b** in 92–93% yield and 61–93% ee. The absolute configuration of the products **29a** and **b** was once again determined by the planar chirality of the ligands **25**, rather than their tetrahedral chirality. However, additions to the *N*-formyl imine of **28b** in the presence of the bulkier ligands (S,R_p)-**24a** and (S,S_p)-**24b** afforded only the *R* enantiomer of the product **29b**, in 90–92% yield and 92–95% ee, indicating that the stereochemical outcome of the reaction in this case was independent of the planar chirality of **24**. This result has been attributed to interactions between the two phenyl substituents in the ligand side chain.

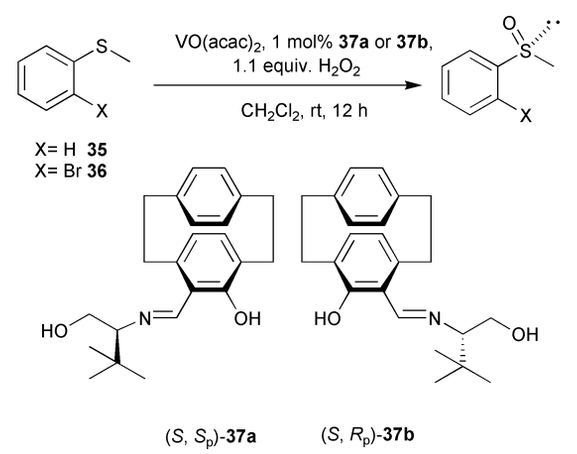
Hou *et al*. have synthesised a series of *N*,*S*- and *N*,*Se*- planar chiral ligands derived from [2.2]paracyclophane and applied them in a palladium catalysed allylic alkylation reaction (Scheme 9).[46]

It was found that using 6 mol% of **31**–**34** afforded the substitution product **30** in almost quantitative yield. However, ligands **32** and **34** achieved 98% conversion in approximately 2 hours as opposed to the 20–40 hours required using **31** and **33**. Moreover, the reaction using **32** provided a far higher level of enantio differentiation in comparison to **31** (94% *vs.* 50–63% ee), and ligand **34** also gave a far higher level of enantioselectivity than **33** (93% *vs.* 57–73%). It was shown that (S,S_p)-**31a** and (S,S_p)-**33a** gave the *R* stereoisomer of the product **30**, whilst (S,R_p)-**31b** and (S,R_p)-**33b** afforded the *S* stereoisomer. The results show that the benzylic substituted ligands **32** and **34** with donor atoms at the benzylic position are more active ligands than **31** and **33** with both coordinating atoms attached to the aromatic ring. Incorporation of heteroatoms at the benzylic position was presumed to create a more active environment for chirality transfer due to the increased tether length between the donor atoms.

Recently Vetter and Berkessel described the synthesis of the Schiff base ligand **37** for the asymmetric sulfoxidation of thioethers **35** and **36** (Scheme 10).[47]



Scheme 9



Scheme 10

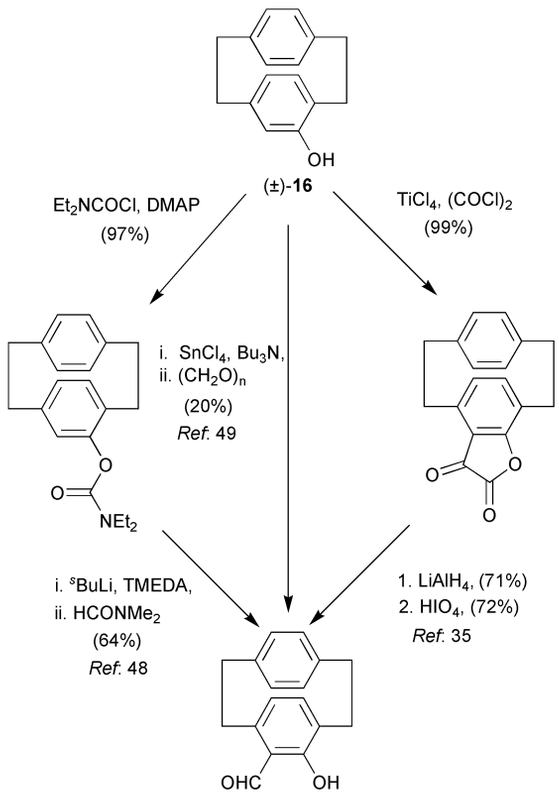
Use of ligand **37a** generated the *R* sulfoxides of thioanisole **35** and *o*-bromothioanisole **36** in 78 and 85% isolated yield respectively, but in extremely disappointing enantiomeric excesses (2–4%). Treatment of the thioethers **35** and **36** with **37b**, however, gave the *S* sulfoxides in significant enantiomeric excesses (46–48%) and improved yields (82–92%).

4.2 Synthetic approaches to enantioenriched ligands

The transition metal based catalysts discussed in Section 4.1 contain disubstituted [2.2]paracyclophane ligands bearing adjacent substituents on the same aromatic ring, several of which are derived from (R_p)-(+)– or (S_p)-(−)-5-formyl-4-hydroxy[2.2]paracyclophane **38**. This section of the review examines the best methods available to obtain enantiomerically enriched **38**, supplemented by a discussion of the synthesis of ligands **31**–**34**, included to demonstrate how benzylic donor atoms have been introduced into [2.2]paracyclophane ligands.

The best approaches to enantiomerically enriched **38** involve resolution of racemic **38** or *ortho*-formylation of enantiomerically enriched 4-hydroxy[2.2]paracyclophane **16**.

Racemic **38** has been synthesised using three methods for the *ortho*-formylation of (±)-4-hydroxy[2.2]paracyclophane **16**. These are summarised in Scheme 11.[35,48,49]



Scheme 11

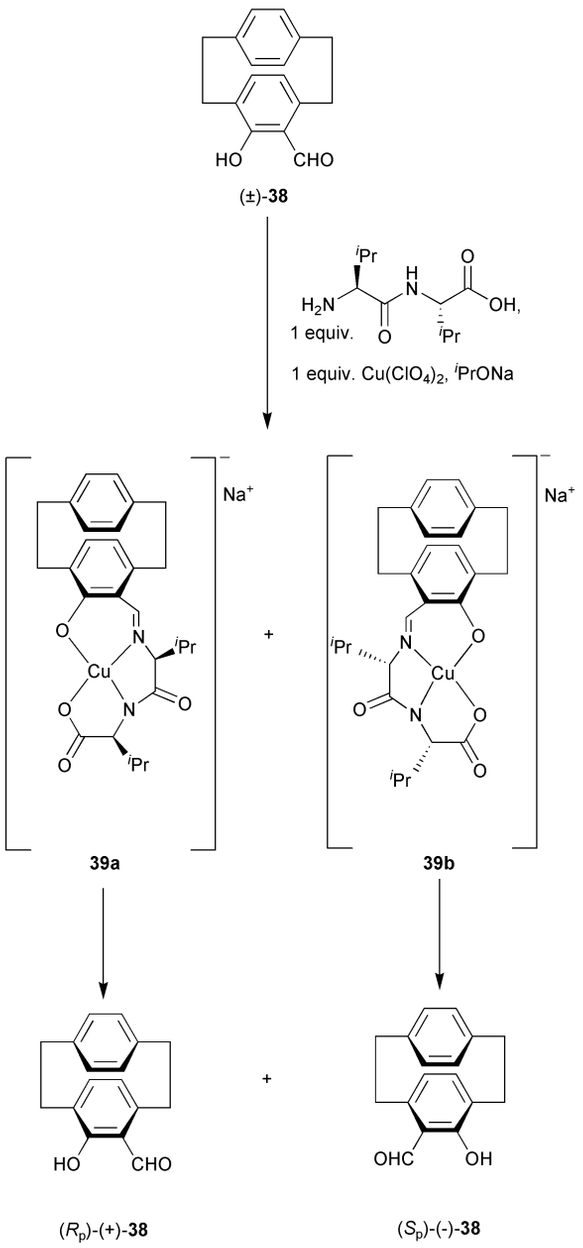
Belekon *et al*. have resolved (±)-**38** *via* complexation with $Cu(ClO_4)_2$ in the presence of H_2N-(*S*)-Val-(*S*)-Val-OH and sodium isopropoxide (Scheme 12).[50]

The least soluble of the two diastereoisomeric complexes formed, **39a**, crystallised from the reaction flask on cooling and was hydrolysed to afford (R_p)-(+)-**38** in 17% yield and 86% ee. The mother liquor was evaporated and chromatographed to afford the Cu(II) complex **39b** which was hydrolysed to afford (S_p)-(−)-**38** in 17% yield and 85% ee. Belekon, Rozenberg *et al.* have reported an alternative approach to the resolution of (±)-**38** using (*R*)-(+)-α-methylbenzylamine.[49] A single crystallisation of the reaction mixture, gave the (R,R_p) diastereoisomer with a de >90% and recrystallisation of this material increased the diastereoisomeric excess to 96%. The imine was hydrolysed using hydrochloric acid to afford (R_p)-(+)-**38** in 33% yield. Hydrolysis of the (R,S_p) diastereoisomer present in the combined mother liquors gave partially resolved (S_p)-(−)-**38**. Hence, this sample of (S_p)-(−)-**38** was combined with (*S*)-(−)-α-methylbenzylamine to give, after crystallisation, the (S,S_p) diastereoisomer. Hydrolysis gave enantiopure (S_p)-(−)-**38** in 25% yield.

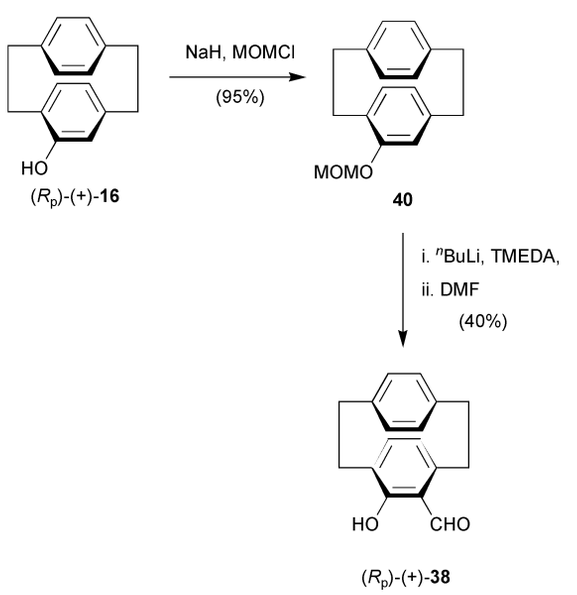
As an alternative to using a resolution approach, Fringuelli *et al*. synthesised (R_p)-(+)-**38** from (R_p)-(+)-**16** by initial protection of the hydroxyl functionality using MOMCl (Scheme 13).[27] A MOM directed *ortho*-lithiation of **40** and subsequent electrophilic quench using dimethylformamide afforded (R_p)-(+)-**38** in 40% yield.

Hopf *et al*. have used a similar synthetic strategy for the synthesis of (R_p)-(+)– and (S_p)-(−)-**38** starting from (R_p)-(+)– and (S_p)-(−)-**16** and adopting the dimethylformamide procedure depicted on the left hand side of Scheme 11.[35]

Examination of the synthesis of the planar chiral *N*,*S* and *N*,*Se*-based [2.2]paracyclophane ligands **31**–**34** used in the

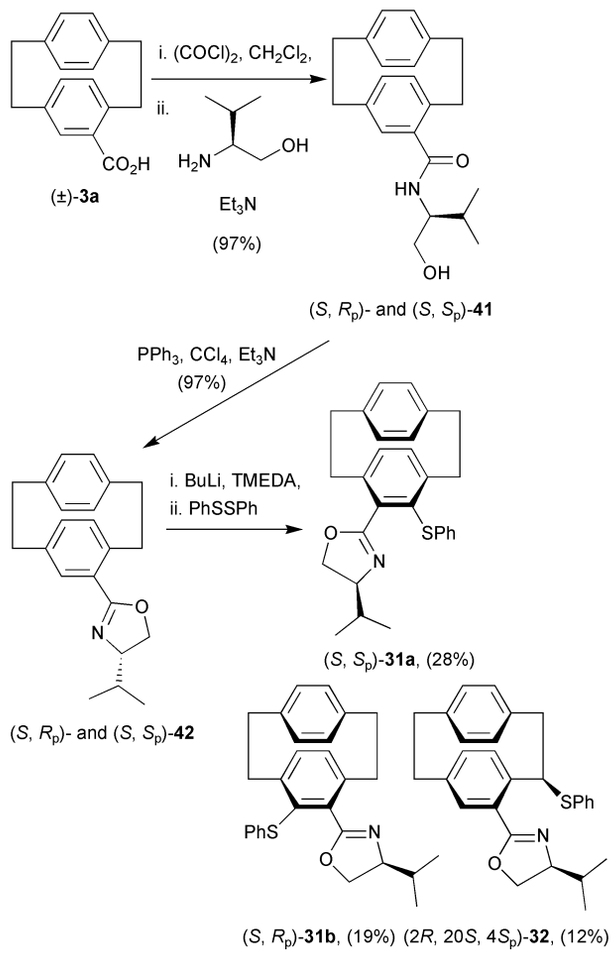


Scheme 12



Scheme 13

palladium catalysed allylic alkylation reactions reported in Section 4.1 reveals not only a slightly different approach to the synthesis of cyclophanes disubstituted on one ring, but also the way in which the unusual benzylic substituted cyclophanes **32** and **34** were formed. Conversion of (±)-**3a** to the corresponding acid chloride and reaction with (*S*)-valinol afforded the diastereoisomers (*S*,R_p)- and (*S*,S_p)-**41** (Scheme 14).



Scheme 14

Subsequent reaction with triphenylphosphine and triethylamine gave the oxazoline derivatives (*S*,R_p)- and (*S*,S_p)-**42**. Treatment of (*S*,R_p)- and (*S*,S_p)-**42** with an equimolar mixture of *n*BuLi and TMEDA at 0 °C, followed by an electrophilic quench using diphenyl disulfide, gave rise to isolated samples of **31a**, **31b** and **32**, in 28, 19 and 12% yield respectively. A similar synthetic procedure was adopted for the synthesis of ligands **33a**, **33b** and **34**, except that the electrophile diphenyl diselenide was used to quench the *ortho*-lithiated derivative of **42**.

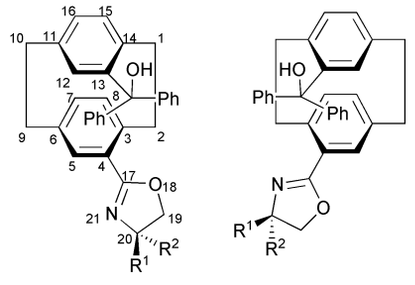
5 [2.2]Paracyclophanes with substituents on both rings

5.1 Applications in asymmetric catalysis

Disubstituted [2.2]paracyclophane derivatives bearing substituents on both aromatic rings have been employed in diethylzinc additions to aldehydes, hydrogenation reactions and palladium catalysed aminations.

The novel *N*,*O*-planar chiral [2.2]paracyclophane ligands **43a**–**d** and **44a**–**d** (Fig. 5) have been tested in diethylzinc additions to aromatic substrates.[51]

Use of 5 mol% of the ligands **43a**–**d** or **44a**–**d** and a ratio of diethylzinc–benzaldehyde of 2.2 afforded poor to excellent enantiomeric excesses for the product ethylbenzyl alcohol **26**. Ligands **43a** and **43c** gave the best yields (93–96%) and enantio-



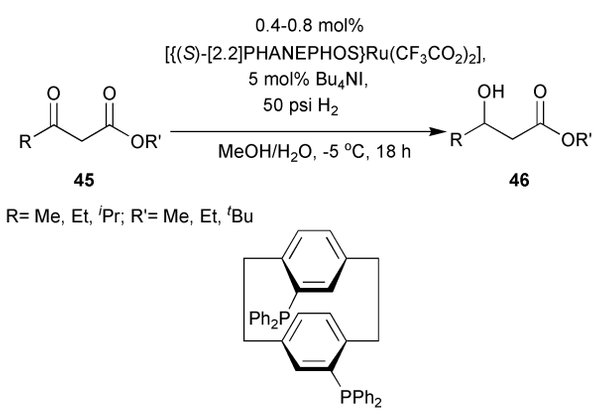
(20*S*, 4S_p, 13R_p)-**43a**-**c** (20*S*, 4R_p, 13S_p)-**44a**-**c**
(20*R*, 4S_p, 13R_p)-**43d** (20*R*, 4R_p, 13S_p)-**44d**

a: R^1= H, R^2= ^{i}Pr; **b**: R^1= H, R^2= ^{t}Bu; **c**: R^1= H, R^2= Bn; **d**: R^1= Ph, R^2= H

Fig. 5

selectivities (93% ee). Ligand **43c** was then screened against a variety of aromatic aldehydes and generated good yields (86–96%) of the secondary alcohol products of *p*-chlorobenzaldehyde, *p*-bromobenzaldehyde, *o*- and *p*-anisaldehyde and β-naphthaldehyde in 94, 93, 81, 82 and 95% ee respectively. Ligands **43a**–**c** and **44d**, all with the same relative stereochemistry, showed higher reactivity and induced higher selectivity than the corresponding diastereoisomers **44a**–**c** and **43d**.

A ruthenium(II) catalyst system based upon (*S*)-4,12-bis-(diphenylphosphino)-[2.2]paracyclophane {(*S*)-[2.2]PHANEPHOS} **47** has been developed for the asymmetric hydrogenation of β-keto esters **45** (Scheme 15).[52]



R= Me, Et, ^{i}Pr; R'= Me, Et, ^{t}Bu

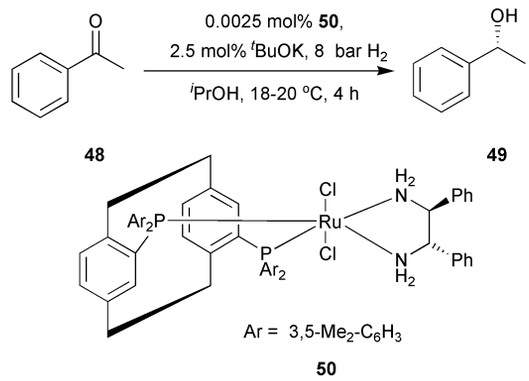
(*S*)-[2.2]PHANEPHOS **47**

Scheme 15

Using 0.4–0.8 mol% of [{(*S*)-[2.2]PHANEPHOS}Ru(CF_3CO_2)$_2$] and 5 mol% of Bu_4NI, all reactions went to completion within 18 h providing β-hydroxy esters **46** in up to 96% ee. The ruthenium(II) diphosphine catalyst is highly active and its use obviates the forcing conditions and high catalyst loadings that were previously employed for the hydrogenation of β-keto esters **45**.[53–55]

After Noyori's discovery that diphosphine ruthenium diamine complexes are very active catalysts for the asymmetric hydrogenation of aldehydes and ketones,[56] Burk *et al.* synthesised a series of PHANEPHOS ruthenium diamine complexes and tested them as reduction catalysts.[57] After an initial screening of ruthenium(II) catalysts containing different diamine ligands with (*S*)-[2.2]PHANEPHOS **47** or (*R*)- or (*S*)-4,12-bis(di-3,5-xylylphosphino)[2.2]paracyclophane {xylyl[2.2]-PHANEPHOS}, the catalyst **50** was identified as the optimum one for the hydrogenation of acetophenone **48** providing **49** in 99% ee and >97% yield on a preparative scale (Scheme 16).

The success of the initial screen prompted an examination of different aromatic, heteroaromatic and α,β-unsaturated ketones. Excellent enantioselectivities were observed for a range of aryl alkyl ketones (94–99%), but the introduction of



48 **49**

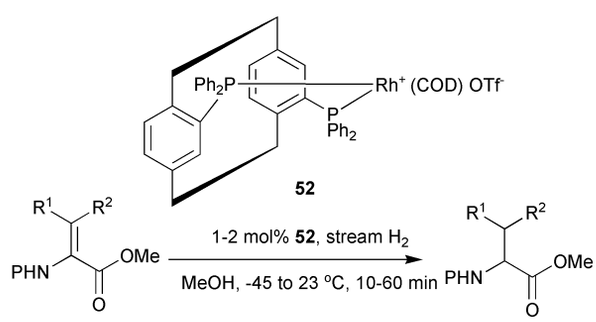
Ar = 3,5-Me_2-C_6H_3

50

Scheme 16

α-branching resulted in reduced enantiomeric excess (31%). In this case switching to the parent PHANEPHOS based catalyst increased the enantioselectivity to 71%. Exchange of the aryl functionality of the ketone **48** for other aromatics such as naphthyl, ferrocenyl, furyl, thienyl and pyridyl also furnished secondary alcohol products with a high degree of enantioselection (78–99%). Examination of α,β-unsaturated ketones with **50** proved fruitful with ee's of 97% and 94% recorded for the allylic alcohols *trans*-(*R*)-4-phenyl-3-buten-2-ol and (*R*)-1-(1′-cyclohexenyl)ethanol. Troublesome dialkyl ketones such as acetylcyclohexane gave a moderate selectivity of 49%.

Pye, Rossen *et al.* have demonstrated that the rhodium(I) (*R*)-[2.2]PHANEPHOS catalyst **52** displays a high level of activity for the asymmetric hydrogenation of dehydroamino acid methyl esters under extremely mild conditions, providing enantioselectivities up to 99.6% for **51a**–**f** (Scheme 17).[58]

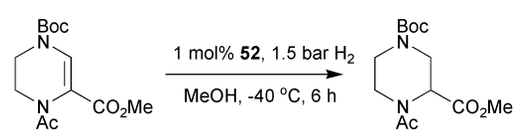


52

51a R^1= H R^2= H P= Ac
51b R^1= Ph R^2= H P= Ac
51c R^1= Me R^2= H P= Ac
51d R^1= Ph R^2= H P= Bz
51e R^1= H R^2= H P= CBz
51f R^1= Me R^2= Me P =Ac

Scheme 17

The pronounced activity of the (*R*)-[2.2]PHANEPHOS catalyst **52** was illustrated by the reduction of tetrahydropyrazine **53** to afford **54**, a precursor of the HIV protease inhibitor Crixivan, in 86% ee and 100% conversion (Scheme 18).



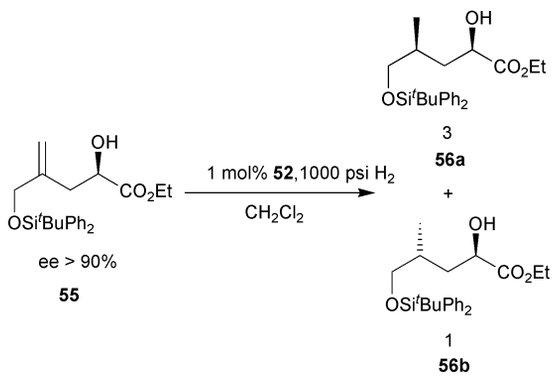
53 **54**

Scheme 18

Previous reductions of **53** using diphosphine rhodium catalysts had required forcing conditions (70 bar, 40 °C, 24 h) and had given moderate levels of enantiomeric purity and

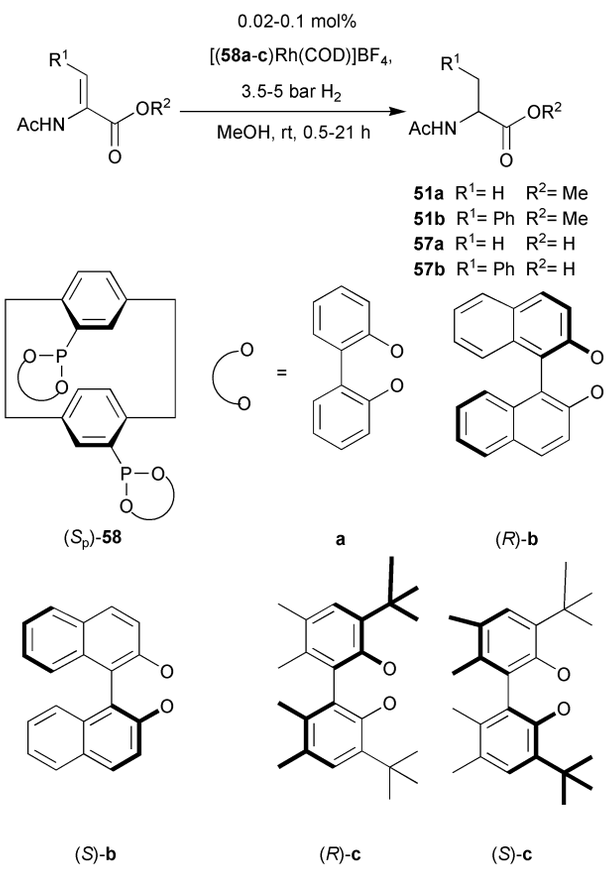
incomplete conversions (*e.g.* BINAP, 56% ee, Et-DUPHOS, 50% ee).[59] An insight into the mechanism of the catalyst has been provided.[60,61]

More recently, catalyst **52** has been employed in the hydrogenation of the enantioenriched homoallylic alcohol **55** *en route* to the bromopyrrole alkaloid Manzacidin A.[62] The product **56a/b** was obtained in a quantitative yield, with a diastereoselectivity of 3 : 1 in favour of the *cis* diastereoisomer **56a** (Scheme 19).



Scheme 19

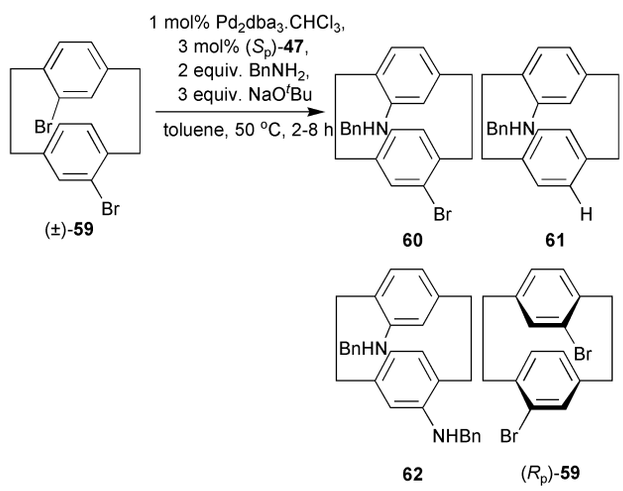
A series of phosphonite ligands (S_p)-**58a**, and (S_p)-**58**-(*R*)-**b**, (S_p)-**58**-(*S*)-**b**, (S_p)-**58**-(*R*)-**c**, (S_p)-**58**-(*S*)-**c** that contain an additional element of axial chirality, have been synthesised and tested in the asymmetric hydrogenation of *N*-acetyl dehydroamino acids and methyl esters (Scheme 20).[63]



Scheme 20

Initially 0.1 mol% of ligand (S_p)-**58a** was used in the hydrogenation of methyl 2-acetamidoacrylate providing (*S*)-**51a** in >99% conversion and an enantiomeric excess of 96% in 0.5 h. Use of 0.1 mol% of (S_p)-**58**-(*R*)-**b** gave a similar result providing (*S*)-**51a** in 99% conversion and 99% ee in 0.5 h. Employment of (S_p)-**58**-(*S*)-**b**, however, resulted in only 5% conversion after 1 h and 98% conversion after 16 h, and a lower level of enantiomeric purity of (*S*)-**51a** (74%). It was thus clear that the combination (S_p)-**58**-(*R*)-**b** led to a highly active rhodium catalyst, whereas (S_p)-**58**-(*S*)-**b**, gave a considerably less active and less selective catalyst. Increasing the bulk of the biaryloxy moiety using (*R*)-**c** meant that a reaction time of 21 h was required to achieve a conversion of just 25% for (*S*)-**51a** with a moderate enantioselection of 46%. A promising level of activity was obtained using lower catalyst loadings. For example, using 0.02 mol% of catalyst (S_p)-**58a** gave a 100% yield of (*S*)-**57b** in 2 h in 95% ee.

Pye, Rossen *et al.* have shown that Pd_2dba_3–(*S*)-[2.2]-PHANEPHOS **47** is an effective catalyst system for the Buchwald–Hartwig amination of (±)-4,12-dibromo-[2.2]paracyclophane **59**, providing a practical kinetic resolution of (±)-**59** to give (R_p)-**59** in high enantiomeric excesses (Scheme 21).[64]



Scheme 21

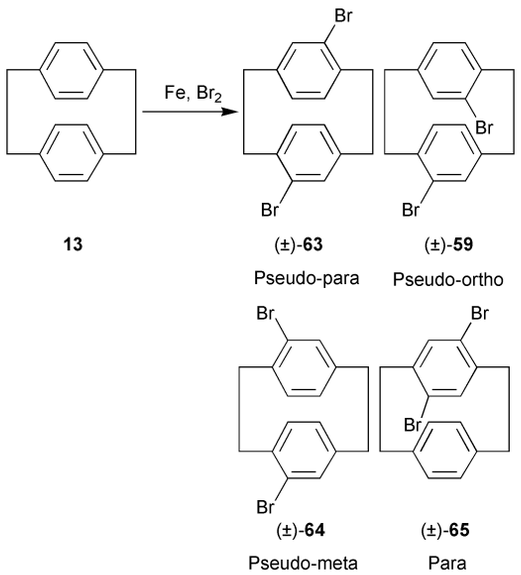
The reaction of (±)-**59** afforded the monosubstitution product **60**, the dehalogenated product **61**, the diamine **62** together with the desired (R_p)-**59**. It was shown that (S_p)-**59** reacts 3 to 4 times faster than (R_p)-**59** at 50 °C. Although the addition of the halide additive $CH_3(CH_2)_{17}NMe_3Br$ had little effect on the reaction, the use of $TlPF_6$ greatly reduced the reaction rate and at the same time increased the enantiomeric discrimination to 10–13:1. Increasing the conversion of the reaction to 90% using $TlPF_6$ afforded the remaining 10% of **59** as (R_p)-**59** in >99.9% ee. A practical process for the production of (R_p)-**59** on a gram scale has emerged from this work: driving the conversion to 79%, gives (R_p)-**59** in 93% ee and 42% yield.

5.2 Synthetic approaches to enantioenriched ligands

The transition metal catalysts discussed in Section 5.1 contain disubstituted [2.2]paracyclophane ligands bearing substituents on both aromatic rings. This area is currently dominated by [2.2]PHANEPHOS **47** and its derivatives, and so this section focuses mainly on the preparation of enantiopure [2.2]-PHANEPHOS **47** and related phosphonite ligands. The synthesis of the *N*,*O*-based [2.2]paracyclophane ligands **43a**–**d** and **44a**–**d**, is also included, however, to illustrate how [2.2]paracyclophane ligands bearing different substituents on their aromatic rings are currently being synthesised.

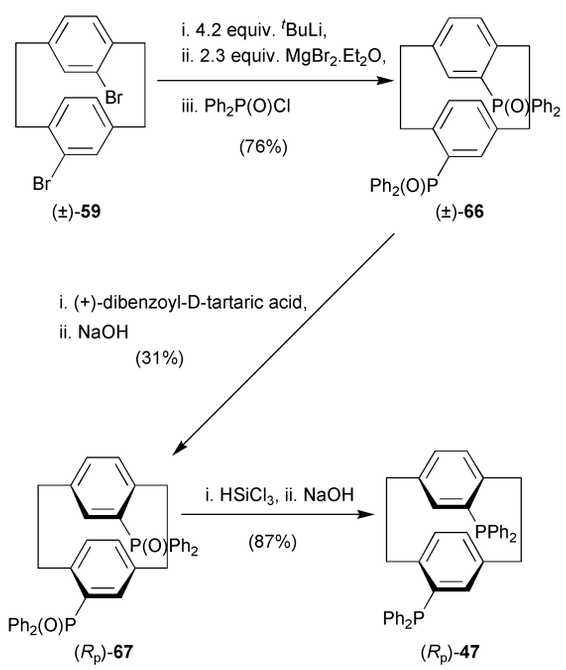
To date the only approach to enantioenriched (R_p)-[2.2]-PHANEPHOS **47** starts with the iron catalysed bromination of [2.2]paracyclophane **13** which gives the dibromides **59** and **63**–**65** (Scheme 22).[58]

The tedious chromatographic isolation of the desired pseudo-*ortho* isomer **59** was avoided by crystallisation of the



Scheme 22

reaction mixture to afford the pseudo-*para* isomer **63**, which subsequently underwent thermal isomerisation at 230 °C to give a 1 : 1 mixture of the pseudo-*ortho* and -*para* regioisomers **59** and **63**. On cooling, the pseudo-*para* regioisomer **63** crystallised, leaving the desired pseudo-*ortho* regioisomer **59** in the mother liquor in >90% purity. Lithiation of (±)-**59** and transmetalation with magnesium bromide, followed by reaction with diphenylphosphinyl chloride afforded (±)-**66** (Scheme 23).

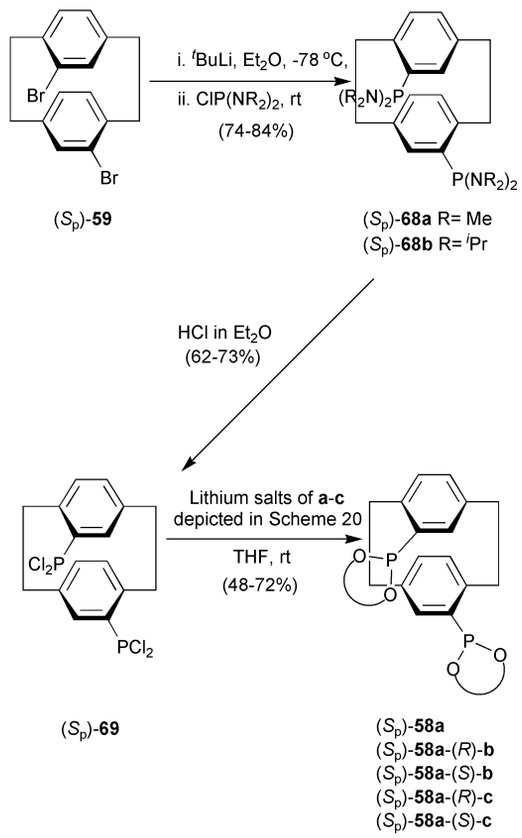


Scheme 23

Resolution of (±)-**66** was achieved by the addition of (+)-dibenzoyl-D-tartaric acid which gave white crystals that on treatment with sodium hydroxide produced (R_p)-**67** in >99.5%. Finally, reduction of (R_p)-**67** with trichlorosilane gave (R_p)-**47**.

Phosphonite ligands have been synthesised from enantiomerically pure (S_p)-pseudo-*ortho*-dibromo[2.2]paracyclophane **59** which was derived from the palladium catalysed amination reaction described in Scheme 21. Lithiation and reaction with a chloro diaminophosphine afforded **68a** and **b** (Scheme 24).[63]

Further treatment with a solution of hydrogen chloride in diethyl ether afforded (S_p)-**69** which was then reacted with a



Scheme 24

range of lithium phenolates to give a series of phosphonite ligands.

The *N*,*O*-based [2.2]paracyclophane ligands **43a**–**d** and **44a**–**d** have been synthesised as follows. Conversion of (±)-**3a** into its acid chloride and reaction with a number of enantiomerically pure amino alcohols **70a**–**d** afforded the diastereoisomeric amides **71a**–**d** (Scheme 25).[51]

An iron catalysed electrophilic substitution with bromine then afforded the diastereoisomeric bromides **72a**–**d**, the cyclisation of which provided the diastereoisomeric pairs of oxazolinylcyclophanes **73a**–**d** and **74a**–**d**, which could be separated by column chromatography. In separate reactions, bromo–lithium exchange and quenching with benzophenone gave the *N*,*O*-based [2.2]paracyclophane ligands **43a**–**d** and **44a**–**d**. The absolute configuration of the products was determined by X-ray crystallographic analysis of **73d** and **74c**.

6 Bipyridine analogues of [2.2]paracyclophane

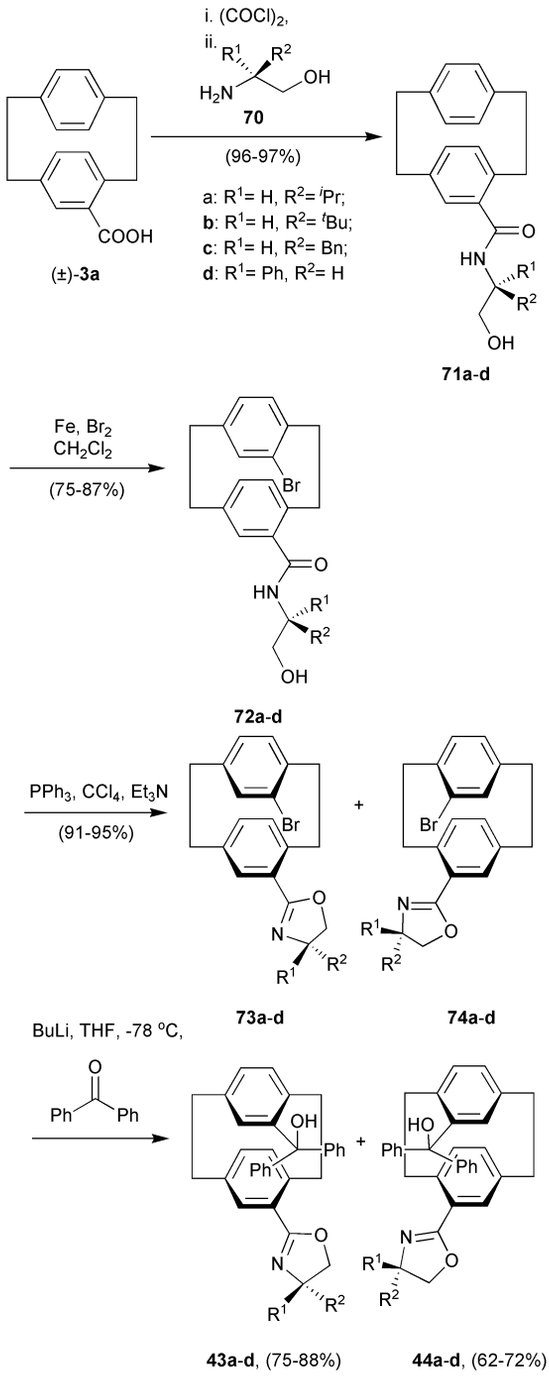
Bipyridine analogues of [2.2]paracyclophane have been employed in cyclopropanations and transfer hydrogenation reactions producing excellent yields and modest enantioselectivities.

The planar chiral ligands **77** and **78** have been used in the copper catalysed asymmetric cyclopropanation of styrene **4** using ethyl diazoacetate **75** (Scheme 26).[65,66] (It was not specified which enantiomer of **77** and **78** was employed.)

Ligand **77** afforded the product **76** in 72% yield with a *trans* : *cis* ratio of 1.9 : 1; the *trans* isomer was formed in 10% ee and the *cis* isomer in 23% ee. Ligand **78** gave the product **76** in 45% yield with a *trans* : *cis* ratio of 2 : 1; the *trans* and *cis* isomers were both produced in 26% ee.

Ligands **77** and **78** have also been employed in the iridium catalysed asymmetric transfer hydrogenation of acetophenone **48** (Scheme 27).[65,66]

Use of ligand **77** for 2 h at room temperature gave the product **49** in 8% yield and with no enantioselection. Raising the



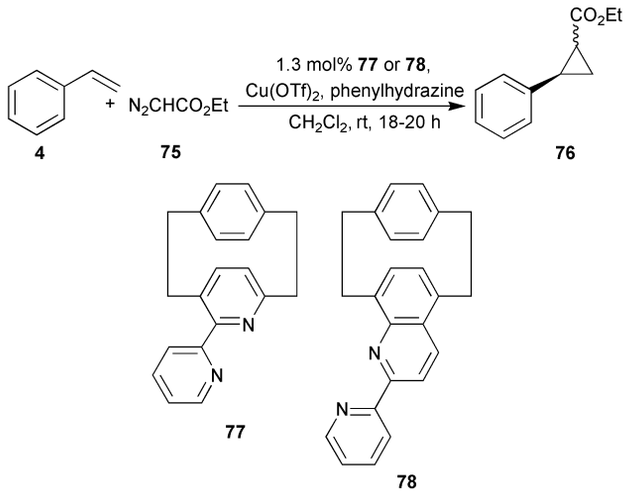
Scheme 25

temperature to 80 °C for 1 h gave **49** in 93% yield and 23% ee. Repeating the reaction with ligand **78** under the original conditions of 2 h at room temperature, gave the product **49** in 49% yield and 25% ee. Increasing the reaction time to 16 h afforded **49** in 91% yield and 31% ee.

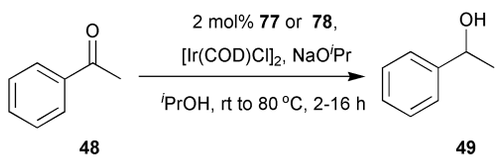
The transition metal catalysts discussed in this section contain planar chiral bipyridine analogues of [2.2]paracyclophane. The syntheses of enantioenriched **77** and **78** are discussed here as they represent an interesting extension of the ligand class to include heterocyclic derivatives.

Racemic pyridinophane **77** has been synthesised starting from commercially available 2,5-pyridinedicarboxylic acid **79** by the route outlined in Scheme 28.[65] It was subsequently resolved by semi-preparative HPLC using a chiral stationary phase column.

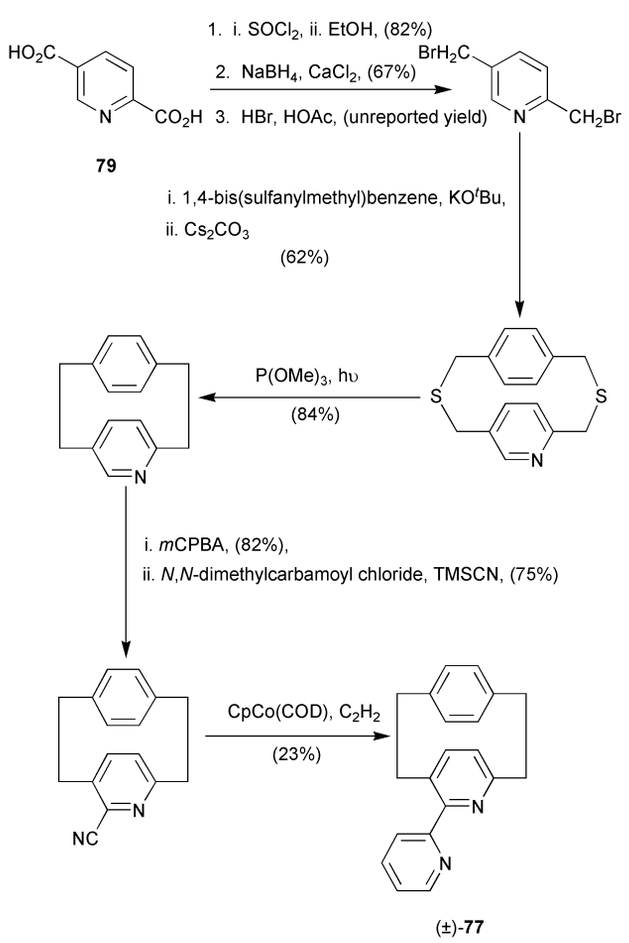
The racemic synthesis of quinolinophane **78** proceeded *via* the NBS-bromination of **80** as shown in Scheme 29.[66] It too was resolved by chiral HPLC.



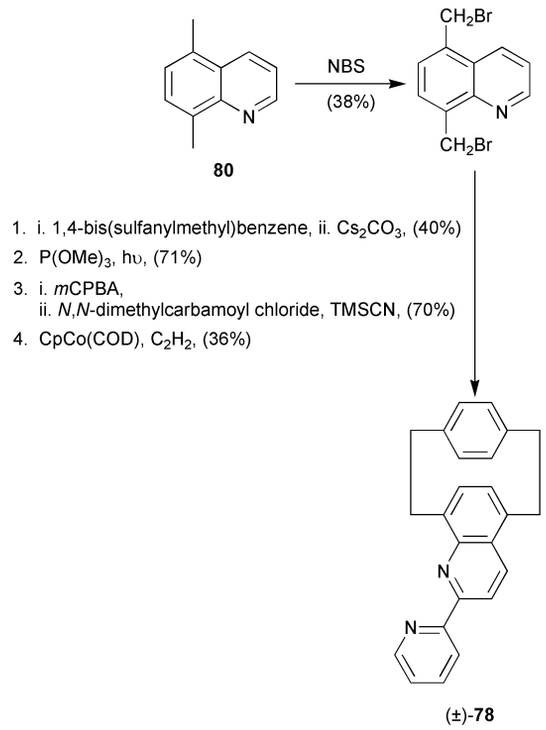
Scheme 26



Scheme 27



Scheme 28



Scheme 29

7 Summary and outlook

This survey of the use of [2.2]paracyclophane derivatives in asymmetric catalysis has revealed that to date a rather limited range of cyclophane ligands has been applied to a fairly wide variety of catalytic oxidations, reductions, and carbon–carbon bond-forming reactions, producing yields and selectivities that range from modest to excellent.

Monosubstituted [2.2]paracyclophane ligands have formed catalysts that are only modestly selective. In contrast, disubstituted cyclophanes with substituents either on the same ring or on different rings have formed some very selective classes of catalyst. Of particular note are the ligands developed by Bräse, depicted in Scheme 6, and the phosphines and phosphonites typified by PHANEPHOS. PHANEPHOS itself has started to find applications in the synthesis of biologically active molecules.

The reactions investigated to date suggest that the creation of cyclophanes bearing chiral substituents leads to an interesting interplay between the planar chirality of the cyclophane and the chirality of the substituent. For example, in many of Bräse's reactions the planar chirality overrides the tetrahedral chirality found in the substituents; elsewhere reactions carried out with the phosphonite ligands depicted in Scheme 20 were rendered more selective by the addition of axial chirality of one sense, and slower and less selective when the opposite sense of substituent axial chirality was used.

It appears that progress in the application of [2.2]paracyclophanes in asymmetric catalysis has been governed to date by the ease or otherwise of synthesising enantiomerically pure [2.2]paracyclophanes. For example, the synthesis of monosubstituted cyclophanes is dominated by classical resolution procedures, an approach that can be tedious and low-yielding. Adventurous investigations such as the use of enzymes to generate the hydroxycyclophane **16**, however, have been rewarded with high yields and selectivities. It is interesting that cyclophanes bearing benzylic substituents have only been applied in catalysis in one study (Scheme 9). The high selectivities obtained in this case suggest that the development of efficient synthetic routes to enantiomerically pure cyclophanes bearing benzylic substituents will prove fruitful.

The results obtained with PHANEPHOS and related compounds suggest that cyclophanes bearing donor atoms on both rings may be viewed as a highly selective class of ligand, comparable with some of the best ligand classes available for asymmetric catalysis such as the binaphthyl backbone of BINAP and the 1,2-disubstituted ferrocene backbone of JOSIPHOS. It is thus of considerable interest to develop new synthetic approaches to chiral cyclophanes bearing both identical and non-identical substituents on their two rings.

Finally the imaginative bipyridine ligand synthesis described in Section 6 suggests that *de novo* syntheses of much more stucturally diverse [2.2]paracyclophane ligands could have a major role to play in the development of applications of [2.2]paracyclophanes in asymmetric catalysis in the near future.

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