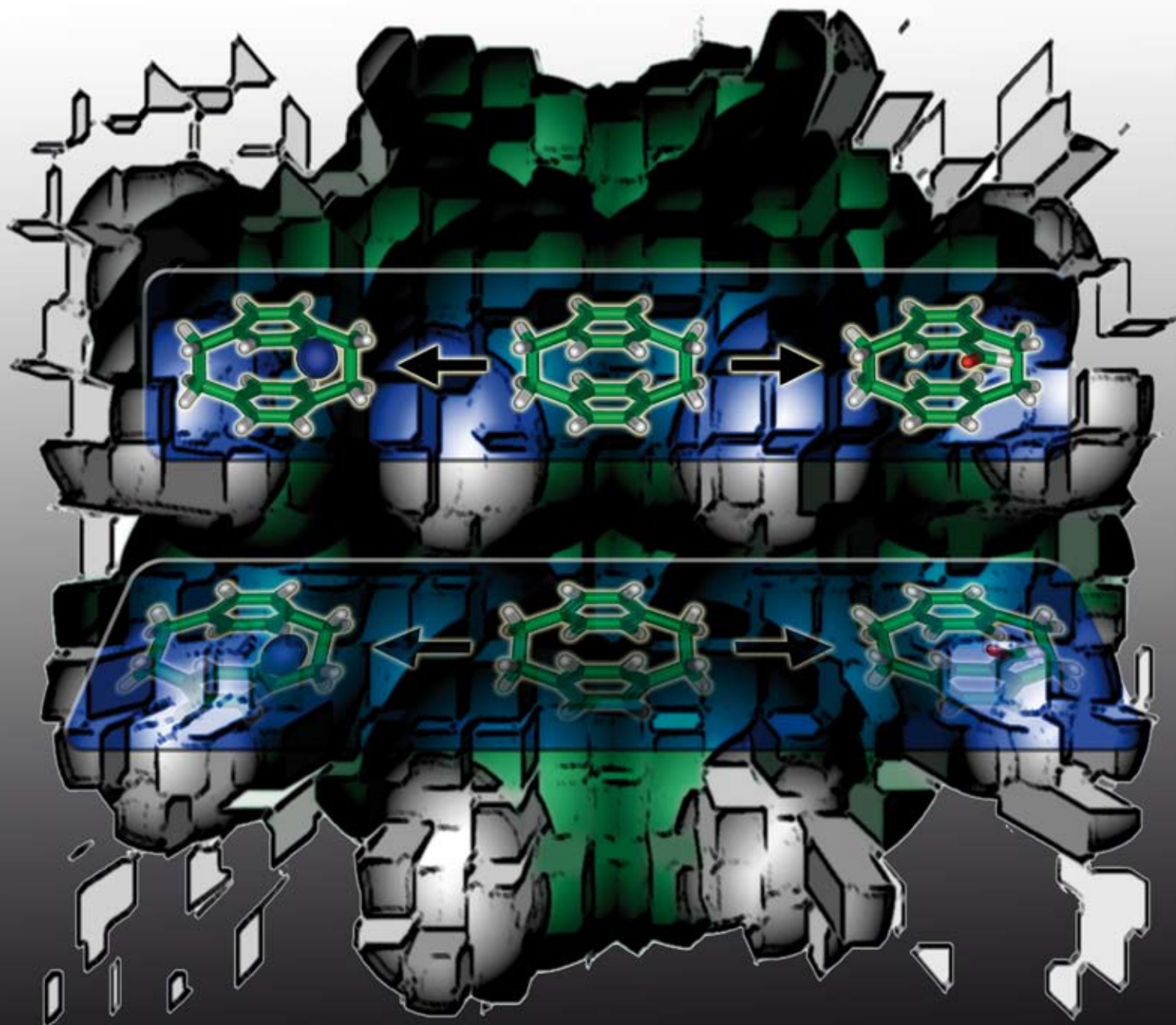


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## EMERGING AREA

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# The synthesis of enantiomerically pure [2.2]paracyclophane derivatives

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[2.2]Paracyclophane is a fascinating molecule that offers great potential in a wide range of chemical disciplines. Currently, the synthesis of the majority of enantiomerically pure [2.2]paracyclophane derivatives is based on the resolution of a small number of starting materials or individual resolution procedures are developed for each new compound. The development of more general routes to these valuable compounds *via* the resolution of a common intermediate is discussed. Ultimately, it would be preferable to synthesise these valuable compounds without recourse to resolution and ideas for this rewarding goal are postulated.

## Introduction

At first glance, the structure of [2.2]paracyclophane (**1a** R = H; Fig. 1) looks surprisingly simple; two eclipsing aryl rings, or decks, held rigidly in place at the *para* positions by ethylene bridges. This useful representation proffers a superficial explanation of the chemistry of these infuriating yet beautiful molecules, but it obscures the unique structure and properties of [2.2]paracyclophane. The proximity of the decks prohibits rotation of the rings without cleavage of one of the bridge C–C bonds, an event that normally does not occur below  $\approx 180$  °C. The separation of the two aromatic rings is less than the sum of the van der Waals radii for carbon (3.40 Å) and ranges from 2.78 Å for the bridgehead carbons (C3–C14) to a maximum of 3.09 Å between C4–C13.<sup>1</sup> The rigid structure results in the bridgehead  $\sigma$  bond (C1–C2 and C9–C10) being held almost perpendicular to the aryl rings allowing a strong  $\sigma_{\text{bridge}}-\pi$  interaction as observed by the lengthening of the C–C bond (1.63 vs. 1.54 Å in ethane). There is a strong repulsion between the two decks resulting in distortion of the aryl rings

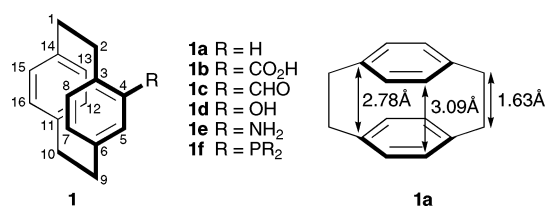


Fig. 1 [2.2]Paracyclophane and derivatives.

to give a shallow 'boat'-like conformation. It also engenders a strong  $\pi$  interaction between the rings that leads to a unique extended  $\pi$ -system. Both its distinct electronic structure and the distortion of the rings increases the basicity/nucleophilicity of [2.2]paracyclophane; it undergoes electrophilic substitution more rapidly than simple aryl systems and has an enhanced ability to form  $\pi$ -complexes; for example, the first order rate constant for the reaction of [2.2]paracyclophane with  $\text{Cr}(\text{CO})_6$  is *ca.* 25% greater than for *p*-xylene.<sup>2</sup>

Like its structure, the chemistry of [2.2]paracyclophane is often understood by the simple representation **1a**; superficially, its reactivity is that of a 'traditional' aromatic compound, albeit that the substituents on one deck have a profound influence on the reactivity of the other deck. But this simplification does not

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always hold up to close scrutiny; due to its distorted structure, steric effects and the unique  $\pi$ -interactions, [2.2]paracyclophane derivatives are often resistant to conventional transformations.<sup>3</sup> It is a combination of all these facets that makes the chemistry of [2.2]paracyclophane such an interesting challenge.

Since its isolation in the middle of the last century,<sup>4</sup> [2.2]paracyclophane has been the focus of numerous studies. Traditionally, [2.2]paracyclophane derivatives have been studied because of their unusual geometry, their steric, transannular and ring strain effects and, as a result, they have had a venerable history as probes for the investigation of theories on bonding, ring strain and  $\pi$  electron interactions.<sup>1,5</sup> Modern applications have seen [2.2]paracyclophane used in biomedical research with various derivatives being employed as bioisoteres for a variety of heterocyclic systems.<sup>6</sup> It is quite remarkable that the relatively bulky [2.2]paracyclophane moiety can be employed as a pharmacophoric element. Even more surprising is the fact that the planar chirality can be exploited in the investigation of stereo-recognition processes at various receptors.

Recent research has seen its properties exploited in two main areas; its electronic properties have been utilised in the design of charge transfer complexes<sup>7</sup> and a variety of molecular electronic materials such as linear and non-linear optoelectronics and conductive polymers.<sup>8</sup> Chiral [2.2]paracyclophane derivatives have found considerable use in stereoselective synthesis and it is this latter application that accounts for the resurgence of interest in [2.2]paracyclophane. The use of [2.2]paracyclophane derivatives as chiral auxiliaries, reagents and ligands has been summarised in two excellent reviews by Gibson<sup>9</sup> and Rozenberg;<sup>10</sup> this article will concentrate on the synthesis of resolved [2.2]paracyclophane derivatives with only a brief précis of their utility.

The majority of [2.2]paracyclophane ligands or reagents are based on one of four different substitution patterns (2–5; Fig. 2); there are examples of derivatives that have been functionalised on the ethylene bridge (6) but these are rare.

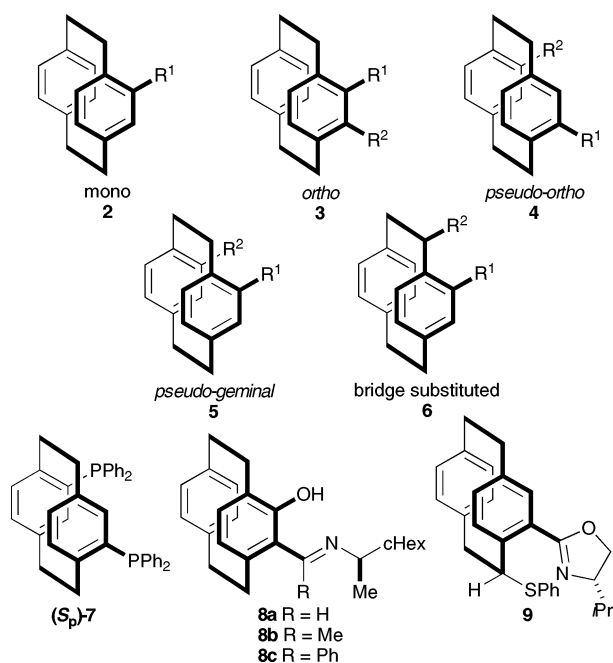


Fig. 2 [2.2]Paracyclophane substitution patterns and ligands.

Prior to the advent of PhanePhos, 4,12-bis(diphenylphosphino)[2.2]paracyclophane **7**, a *pseudo-ortho* disubstituted derivative, as chiral ligand in 1997,<sup>11–13</sup> reports on the use of [2.2]paracyclophane in stereoselective synthesis were scarce. Undoubtedly, it is the great success of PhanePhos in enantioselective hydrogenations that has fuelled research into the utility of [2.2]paracyclophane as a scaffold for the preparation of chiral ligands.

Unlike other common planar chiral scaffolds, such as metallocenes or metal–arene complexes that require two (or more) substituents on one ring to become chiral, [2.2]paracyclophane only requires one substituent to break the symmetry of the molecule. A number of monosubstituted [2.2]paracyclophane (**2**) derivatives have been screened in enantioselective catalysis but the majority show moderate to low enantioselectivities, presumably due to excessive conformational freedom.<sup>14</sup>

Probably the most studied substitution pattern is the *ortho* disubstituted [2.2]paracyclophanes (**3**) due to the ease of their preparation from monosubstituted derivatives. Amongst the most successful *ortho*-disubstituted [2.2]paracyclophane ligands are the 4-hydroxy[2.2]paracyclophane aldimine **8a** and ketimines **8b,c** ligands of Bräse (Fig. 2).<sup>15,16</sup> These ligands are amongst the most successful known for the 1,2-addition of alkyl-, alkenyl- and alkynylzinc reagents to aromatic and aliphatic aldehydes and imines. They can be considered benchmarks not only for the success of [2.2]paracyclophane-based ligands but in the addition of functionalised zinc reagents in general.

The synthesis of *pseudo-geminal* or 4,13-disubstituted [2.2]paracyclophane derivatives (**5**) from monosubstituted starting materials is also relatively simple; the transannular effect facilitates regioselective bromination. As a result, a large number of such ligands have been reported with varying degrees of success in enantioselective catalysis.<sup>17,18</sup>

Functionalisation of the bridging ethylene units is extremely rare (**6**) and to our knowledge only Hou *et al.* have investigated the activity of such compounds as ligands.<sup>19</sup> Significantly, sulfide **9** was found to form a more reactive and more selective catalyst than the *ortho*-disubstituted analogue in palladium-catalysed allylic alkylation reactions (94% vs. 50–63% ee). It is believed that the bridge-substituted ligand **9** possesses a greater degree of flexibility than the *ortho* substituted derivative and is therefore able to adopt a more favourable conformation on complexation. It should be noted that **9** was an unexpected side-product in the synthesis of the *ortho* substituted derivative!

## Synthesis of enantiomerically pure [2.2]paracyclophane derivatives

Arguably the major impediment to the wider acceptance of [2.2]paracyclophane-based ligands is the lack of attractive strategies for the preparation of enantiopure derivatives; the area is still dominated by tedious and frequently expensive resolution protocols. The majority of [2.2]paracyclophane derivatives are prepared from a small pool of compounds. Currently, there are no efficient general routes to a range of [2.2]paracyclophane compounds from a common enantiomerically pure precursor. Below is a summary of the common routes to the resolved compounds.

There are two routes to enantiomerically pure PhanePhos **7**; the first reported synthesis of PhanePhos proceeded *via* the racemic phosphine oxide and resolved this intermediate as diastereoisomeric tartrate salts.<sup>13</sup> PhanePhos is also prepared from enantiomerically pure 4,12-dibromo[2.2]paracyclophane, which is obtained by either chiral chromatography or *via* the kinetic resolution of the dibromide by Hartwig–Buchwald amination.<sup>12</sup> Ironically, the optimum catalyst for the latter procedure appears to be PhanePhos itself. The vast majority of *pseudo-ortho* substituted [2.2]paracyclophane derivatives (**4**) are prepared from this dibromide.

The majority of mono- (**2**) and *ortho* di-substituted [2.2]paracyclophanes (**3**) are prepared from a handful of enantiomerically pure monosubstituted intermediates. The optimum routes to these key compounds appear to be: carboxylic acid **1b** (R = CO<sub>2</sub>H; Fig. 1) *via* recrystallisation of diastereoisomeric (*p*-nitrophenyl)ethylammonium salts;<sup>20</sup> each enantiomer of the aldehyde **1c** (R = CHO) *via* multiple recrystallisations of different Schiff bases<sup>21</sup> or enzymatic methods;<sup>22</sup> phenol **1d** (R = OH) *via* esterification with (*S*)-(–)-camphanoyl chloride and multiple recrystallisations<sup>23</sup> or enzymatic resolution of the acetate;<sup>24</sup> amine **1e** (R = NH<sub>2</sub>) *via* multiple recrystallisations of the diastereoisomeric salts formed from (*S*)-(+)-10-camphorsulfonic acid.<sup>25</sup> Enantiomerically pure 4-phosphino[2.2]paracyclophanes **1f** can be prepared from enantiomerically pure 4-hydroxy[2.2]paracyclophane **1d** but this methodology is long and cumbersome. A more efficient synthesis involves the resolution of racemic phosphine *via* the formation of the diastereoisomeric palladium complexes with the appropriate chiral palladacycle.<sup>14</sup> 4-Bromo[2.2]paracyclophane is now available in enantiomerically pure form *via* an elegant kinetic resolution based upon the Hartwig–Buchwald amination protocol.<sup>16</sup>

A common method for the formation of enantiomerically pure [2.2]paracyclophane derivatives is to incorporate a second stereogenic element into the molecule and then resolve the resulting diastereoisomers. The hydroxy imine ligands of Bräse

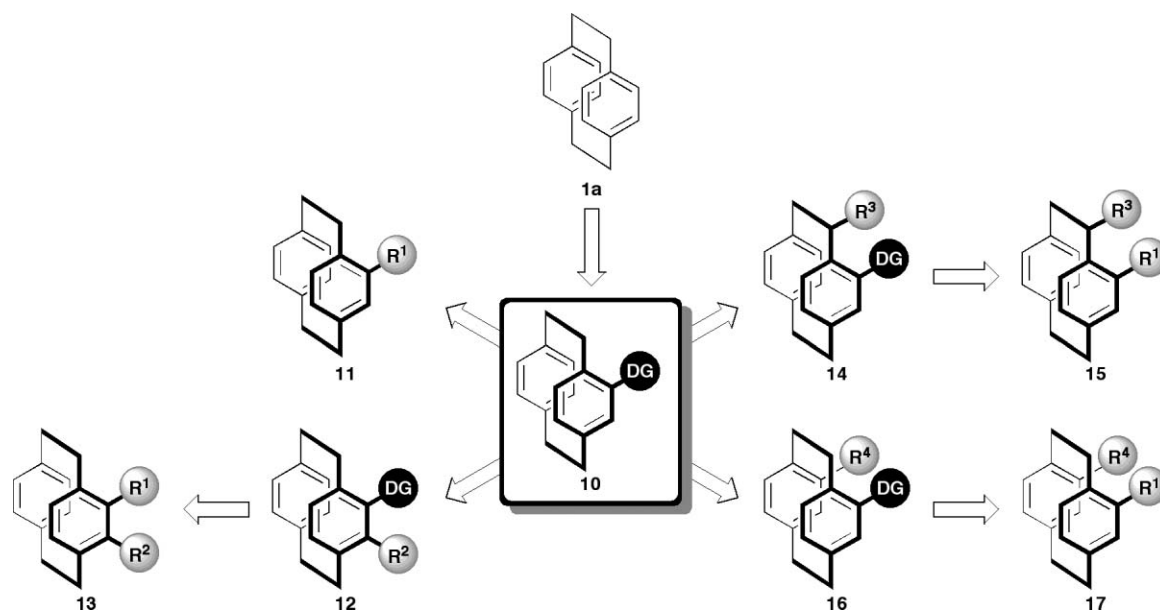
and co-workers,<sup>15,16</sup> **8**, can be prepared in such a manner. Similarly, oxazoline-based [2.2]paracyclophane derivatives, such as **9** are invariably synthesised from the racemic carboxylic acid and only resolved after the formation of diastereoisomeric oxazolines.<sup>18,19</sup>

Hopefully, it is clear that the majority of enantiomerically pure derivatives are either prepared from a small pool of resolved starting materials, or that each new compound requires its own resolution protocol. Furthermore, we and others have found that a number of the known resolution strategies are inefficient and can be quite scale-dependent. As a result we have become interested in the development of a general strategy for the formation of a range of enantiomerically pure [2.2]paracyclophane derivatives from a common precursor.

### Sulfoxide-based methodology

A strategy that permits the synthesis of any of the common [2.2]paracyclophane substitution patterns in enantiomerically pure form from a common precursor with no trace of the resolving/directing group would be highly attractive. Whilst we have yet to achieve this challenging goal, this article shows that we have started to develop the necessary tools to realise this target.

Successful implementation of this strategy requires a multi-purpose directing group that can be readily introduced and will facilitate resolution of the planar chirality (**10**; Scheme 1). The group must possess a number of features; it should permit regioselective elaboration of the [2.2]paracyclophane framework and should either undergo direct substitution or direct elimination so that it can be removed without trace. Such a group combining these characteristics would facilitate the formation of a variety of substitution patterns. Direct displacement would furnish mono-substituted derivatives **11** whilst, directed *ortho*-metallation would permit the formation of **12**, which could readily be converted to *ortho*-disubstituted [2.2]paracyclophane derivatives **13**. Directing metallation to the bridge would allow the formation of **14** and **15**. Whilst the ability to direct functionalisation to the second

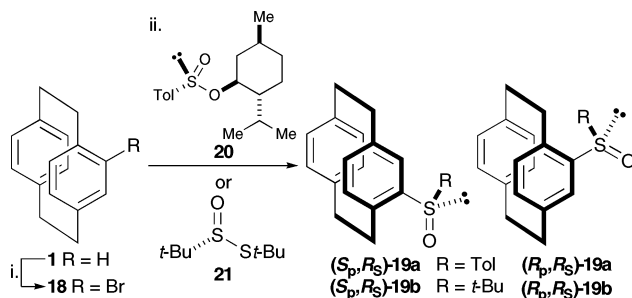


**Scheme 1** General strategy for the synthesis of enantiomerically pure [2.2]paracyclophane derivatives.

ring would allow access to **16** and *pseudo-geminal* compounds such as **17**. Altering the order of elaboration would permit other substitution patterns, such as *pseudo-ortho* **4**, to be prepared.

Of all the possible chiral directing groups, the sulfoxide moiety was deemed the most likely to fulfil all of these criteria. The potential of the sulfinyl moiety has already been demonstrated in Kagan and co-workers' seminal work on the synthesis of chiral ferrocene derivatives.<sup>26</sup> Additionally, Reich and Yelm have used the sulfinyl group to resolve [2.2]paracyclophane during studies on chiral selenides.<sup>27</sup> Inspired by these two reports, we decided to ascertain if the sulfoxide moiety would permit the realisation of our goal.

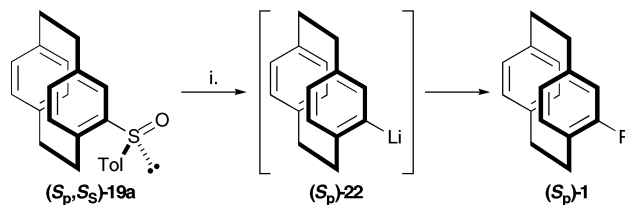
The diastereoisomeric sulfoxides **19a** or **19b** are readily prepared from [2.2]paracyclophane and either the Andersen reagent, (1*S*,2*R*,5*S*)-(–)-menthyl (*R*)-*p*-toluenesulfonate **20**<sup>27–29</sup> or the thio-sulfonate **21** (Scheme 2).<sup>30,31</sup> The stereospecific sulfonylation proceeds with inversion of the sulfur stereocentre and furnishes (*S<sub>p</sub>*,*R<sub>S</sub>*)-**19** and (*R<sub>p</sub>*,*R<sub>S</sub>*)-**19** in a 1 : 1 ratio; these compounds only differ by the planar chirality and hence the orientation of the sulfinyl oxygen. This disparity can be employed to selectively functionalise either the aryl ring (C5) or the bridge (C2). The diastereoisomers are readily separable by column chromatography, even on a 10 gram scale, thereby allowing effective resolution. Initially, the tolylsulfinyl moiety was investigated due to its success in the ferrocene system and the commercial availability of both enantiomers of the Andersen reagent.



**Scheme 2** Synthesis of 4-sulfinyl[2.2]paracyclophane derivatives. Reagents: i. Fe-Br<sub>2</sub> (98%); ii. (a) *n*-BuLi (1.05 eq.), (b) **20** (61%) or **21** (72%).

Key to the success of this methodology is the ability to directly replace the sulfoxide moiety; other auxiliaries have been employed to resolve the planar chirality of [2.2]paracyclophane, but all have

been retained in the final product or have required several steps to remove. Fortunately, sulfoxide–lithium<sup>32</sup> exchange permits the formation of the putative 4-lithio[2.2]paracyclophane **22**, which can react with a range of electrophiles to give enantiomerically pure monosubstituted [2.2]paracyclophane derivatives in good to moderate yields (Scheme 3; Table 1).



**Scheme 3** Synthesis of enantiomerically pure monosubstituted [2.2]paracyclophanes. Reagents: i. (a) *t*-BuLi (4 eq.), (b) electrophile (8 eq.).

The most striking feature of the results in Table 1 is not that the 'sulfoxide methodology' compares favourably with the known resolution strategies for the most common building blocks (Entries 1, 4, 5 and 8) but that all these compounds can be prepared in enantiomerically pure form from the same precursor; there is no need to develop a new resolution protocol for each one. Whilst this methodology is still a resolution, it is still significant for two reasons: its versatility and the lack of the sulfoxide moiety in the final product—the sulfoxide is a 'traceless' resolving agent.

To improve the efficiency of the methodology a stereoconvergent strategy, in which both diastereoisomeric sulfoxides are converted to the *same enantiomer* of 4-monosubstituted [2.2]paracyclophane was investigated. One diastereoisomer would be subjected to sulfoxide–lithium exchange (**10** → **11**; Scheme 1) whilst the other diastereoisomer would employ the 'transannular effect' to direct functionalisation to the *pseudo-geminal* (C13) position before undergoing reductive desulfonylation (**10** → **16** → **11**; Scheme 1). Whilst it is conceivable to achieve the same goal by sulfoxide-directed *ortho* lithiation (**10** → **12** → **11**), non-regioselective deprotonation was an issue.<sup>29</sup>

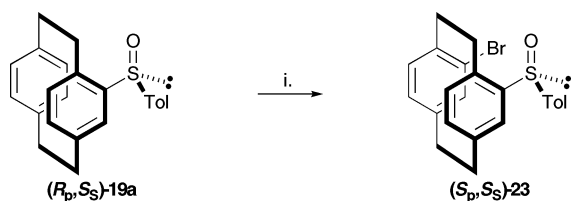
Many electron withdrawing substituents are known to direct electrophilic aromatic substitution to the thermodynamically less stable *pseudo-geminal* position on the second ring.<sup>1</sup> Whilst this effect is often ascribed to the electronic 'transannular effect' there is a strong conformational effect; the substituent must be able to adopt the necessary geometry to abstract the proton from the *pseudo-geminal* position. Thus groups such as acetyl, amide

**Table 1** Synthesis of enantiomerically pure monosubstituted [2.2]paracyclophanes

Entry	Electrophile	Product	R	Yield	Yield <sup>a</sup> (this methodology)	Yield <sup>a</sup> (previous resolutions)
1	DMF	<b>1c</b>	CHO	81	25	20 <sup>22</sup>
2	MeI	<b>1g</b>	Me	64	—	—
3	TMSCl	<b>1h</b>	TMS	44	—	—
4	CO <sub>2(s)</sub>	<b>1b</b>	CO <sub>2</sub> H	77	24	24 <sup>20</sup>
5	B(OMe) <sub>3</sub>	<b>1d</b>	OH	53 <sup>b</sup>	16	11 <sup>23</sup>
6	Ph <sub>2</sub> P(O)Cl	<b>1i</b>	P(O)Ph <sub>2</sub>	52	—	—
7	Ph <sub>2</sub> PCl	<b>1i</b>	P(O)Ph <sub>2</sub>	90 <sup>c</sup>	—	—
8	TsN <sub>3</sub>	<b>1e</b>	NH <sub>2</sub>	32 <sup>d</sup>	10 <sup>d</sup>	24 <sup>25</sup>

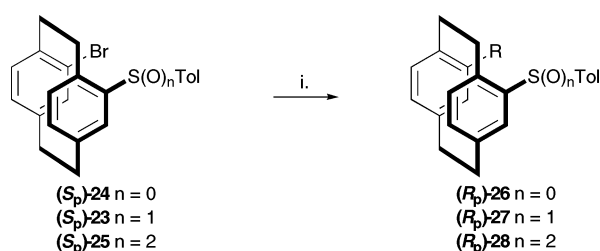
<sup>a</sup> Overall yield from racemic (±)-4-bromo[2.2]paracyclophane to one enantiomer of product. <sup>b</sup> Boron adduct was not isolated but oxidised *in situ* with NMO. <sup>c</sup> Phosphine is believed to oxidise on purification. <sup>d</sup> The low yield is due to a problematic reduction of 4-azido[2.2]paracyclophane, which occurs in only 40%.

and oxazolines are able to direct to this position whilst powerful electron withdrawing groups such as the cyano group are not. Reich and Yelm had previously shown that the sulfone group could direct bromination but there had been no reports of the sulfinyl group being used.<sup>27</sup> Standard iron-catalysed bromination of (*R<sub>p</sub>,S<sub>s</sub>*)-**19a** furnishes **23** in 54% (Scheme 4). Attempts to force the reaction to completion result in reduction of the sulfoxide to the sulfide with concomitant activation of the [2.2]paracyclophane system and multiple brominations.



**Scheme 4** Bromination of the lower ring. Reagents: i. Fe-Br<sub>2</sub> (54%).

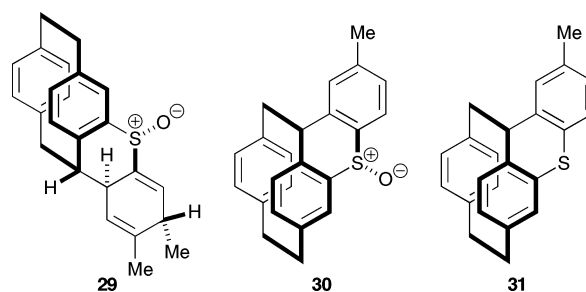
Selective halogen-metal exchange of **23** proved problematic with considerable amounts of [2.2]paracyclophane being isolated, suggesting that the sulfoxide moiety also undergoes a facile exchange process. As a result, conversion of the sulfoxide to either the sulfide **24** or the sulfone **25** prior to halogen-metal exchange was investigated. The halogen-metal exchange of **24** is highly capricious for no discernible reason; the exchange occurs without issue but the fate of the anion is unpredictable. Yields of the desired products range from 0 (only the unsubstituted sulfide observed) to 88% (**26**; R = P(O)Ph<sub>2</sub>; Scheme 5) but are not reproducible. The sulfone **25** shows more promise; halogen-metal exchange followed by reaction with iodomethane leads to the consistent formation of **28** (R = Me). Unfortunately, we have yet to attempt the reductive desulfonylation of **28** but these results provide the foundations for a stereoconvergent route to enantiomerically pure 4-monosubstituted [2.2]paracyclophane derivatives.



**Scheme 5** Functionalisation of the lower ring. Reagents: i. (a) *n*-BuLi, *t*-BuLi or *i*Pr(*n*-Bu)<sub>2</sub>MgLi, (b) electrophile.

Whilst it is impossible to use the tolyl sulfoxide to direct *ortho*-metallation to the C5 position due to the stability of the tolyl *ortho*-anion and the associated problems with regioselectivity, selective deprotonation of the bridge CH<sub>2</sub> is possible. García Ruano has shown that tolyl sulfoxides can stabilise a benzyllithium carbanion in preference to *ortho*-lithiation.<sup>33</sup> Concern about the decreased acidity of the protons of the bridge due to the constrained shape of [2.2]paracyclophane appear to be unfounded; accidental deprotonation of the bridging ethylene unit has been reported independently by Hou,<sup>19</sup> Pelter<sup>34</sup> and Bolm,<sup>35</sup> as has the

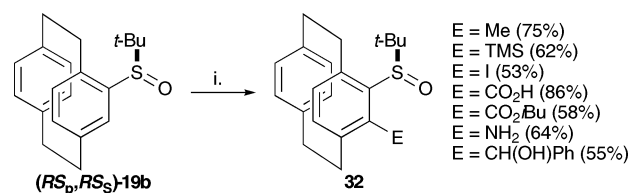
deliberate 'lateral' functionalisation of this position by Hopf and Snieckus.<sup>36</sup> Unfortunately, whilst the tolylsulfinyl moiety is capable of directing 'lateral' lithiation to the bridging unit the tolyl group is not an innocent bystander. Under optimised conditions a mixture of unreacted starting material and various polycyclic compounds (**29–31**) resulting from reaction of the anion with the toluene ring were observed (Fig. 3).



**Fig. 3** Cyclisation on to toluene moiety.

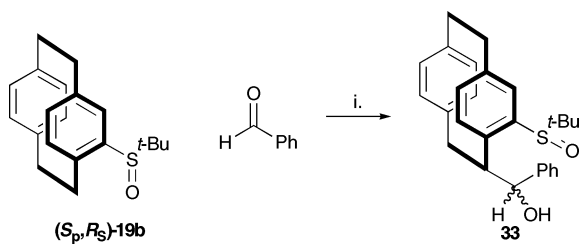
4-Tolylsulfinyl[2.2]paracyclophane shows the potential of the sulfoxide methodology to deliver a range of enantiomerically pure [2.2]paracyclophane derivatives *via* simple chemistry from a diastereoisomeric pair of intermediates. Unfortunately, our initial foray into this chemistry was limited, not by the strategy, but by the reactivity of the toluene substituent, a problem not encountered in the analogous ferrocenyl systems.<sup>26</sup> Replacing the reactive toluene moiety with the more robust *tert*-butyl group has allowed many of these limitations to be overcome but at a price.<sup>30</sup>

As the *tert*-butyl group has no acidic protons there are no issues of regioselectivity in the *ortho*-lithiation reaction and the C5 position can be readily functionalised with a range of electrophiles (Scheme 6). Aldehydes undergo highly diastereoselective addition to give just one stereoisomer. It is clear that both the *tert*-butylsulfinyl moiety and the [2.2]paracyclophane skeleton can act as considerable steric buttresses, not only allowing this highly stereoselective addition to occur but retarding the rate of many of the reactions. Furthermore, elaboration of disubstituted derivatives has proven taxing. This is highlighted by our inability to methylate 5-amino-4-*tert*-butylsulfinyl[2.2]paracyclophane **32** (E = NH<sub>2</sub>) under a variety of conditions including treatment with iodomethane, reductive amination or the use of Meerwein's salt (Me<sub>3</sub>OBF<sub>4</sub>).



**Scheme 6** *ortho* Functionalisation of 4-sulfinyl[2.2]paracyclophane. Reagents: i. (a) *n*-BuLi (2 eq.), (b) electrophile (4 eq.).

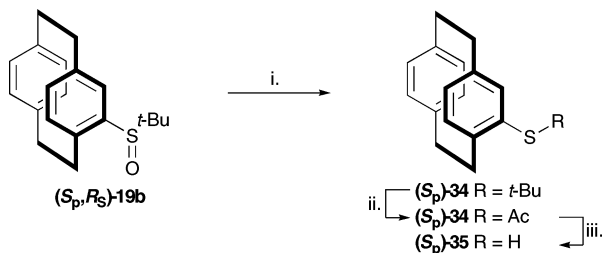
The other sulfoxide diastereoisomer (*S<sub>p</sub>,R<sub>s</sub>*)-**19b** permits lateral functionalisation of the bridge position. Currently, this reaction has not been fully optimised but we have shown that iodomethane and simple aromatic aldehydes undergo addition to give compounds such as **33** (Scheme 7). The addition occurs



**Scheme 7** 'Lateral' functionalisation of 4-sulfinyl[2.2]paracyclophane. Reagents: i. (a) *n*-BuLi (2 eq.), (b) PhCHO (3 eq.) (30%).

with complete stereoselectivity at the bridge position but little or no stereoselectivity at the alcohol.

The *tert*-butylsulfinyl moiety overcomes a number of the problems encountered in the tolyl methodology but it is not without its own shortcomings; the *tert*-butyl derivative is resistant to sulfoxide–metal exchange, its bulk prevents attack of an organometallic reagent. Regioselective bromination of the *pseudo-geminal* position has also proved impossible with decomposition of the sulfoxide occurring under a range of conditions. Removal of the *tert*-butyl moiety can be achieved presenting a novel route to enantiomerically pure [2.2]paracyclophane-4-thiol, a potentially useful intermediate for the preparation of chiral auxiliaries or reagents.<sup>37</sup> Reduction of the sulfoxide **19b** to the sulfide **34** is achieved with trichlorosilane (Scheme 8). A two-step procedure then cleaves the *tert*-butyl group *via* acetylation<sup>38</sup> and hydrolysis to give **35** in moderate yield.

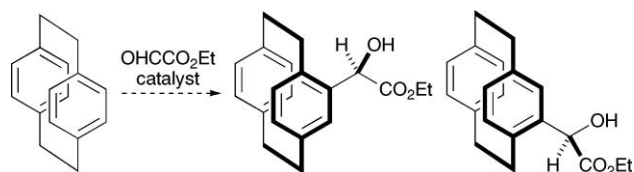


**Scheme 8** Synthesis of [2.2]paracyclophanyl-4-thiol. Reagents: i. HSiCl<sub>3</sub> (15 eq.), Et<sub>3</sub>N (10 eq.) (45%); ii. AcCl (7 eq.), BBr<sub>3</sub> (1.1 eq.) (68%); iii. K<sub>2</sub>CO<sub>3</sub>, MeOH (97%).

It is clear that the sulfoxide-based methodology has the potential to offer a versatile route to a range of enantiomerically pure [2.2]paracyclophane derivatives. This potential has been ably demonstrated by our ability to prepare enantiomerically pure mono-, *ortho* di-, *pseudo-gem* di- and bridge di-substituted [2.2]paracyclophane derivatives. Unfortunately, both sulfoxide derivatives so far tested have certain limitations; the reactivity of the toluenesulfinyl compound prevents directed metallations whilst the inability of the *tert*-butylsulfinyl derivative to undergo sulfoxide–metal exchange frustrates the development of a 'traceless' resolving agent. By investigating other sulfoxide substituents we hope to be able to overcome these shortcomings and develop a truly general route to enantiomerically pure [2.2]paracyclophane compounds.

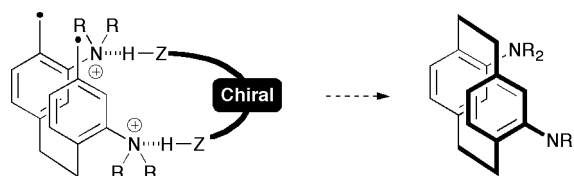
## Non-resolution routes to enantiomerically pure [2.2]paracyclophane derivatives

The sulfoxide-based methodology is still based on resolution and, as such, is not ideal. It would be more attractive if the initial functionalisation of [2.2]paracyclophane furnished only one enantiomer or a single diastereoisomer thus eliminating the inherent redundancy involved in resolution. To our knowledge such a strategy has not been successfully implemented. It is conceivable that this could be achieved *via* an enantioselective variant of the Friedel–Crafts alkylation or an analogous transformation. Enantioselective Friedel–Crafts alkylations are known, but all examples form the new stereocentre on the incoming alkyl fragment and not on the aryl donor.<sup>39</sup> As such, this offers an intriguing challenge. Even if the reaction only controlled the alkyl stereocentre and furnished separable diastereoisomers, this would still offer a rapid route to valuable intermediates (Scheme 9).



**Scheme 9** Resolution *via* enantioselective Friedel–Crafts reaction.

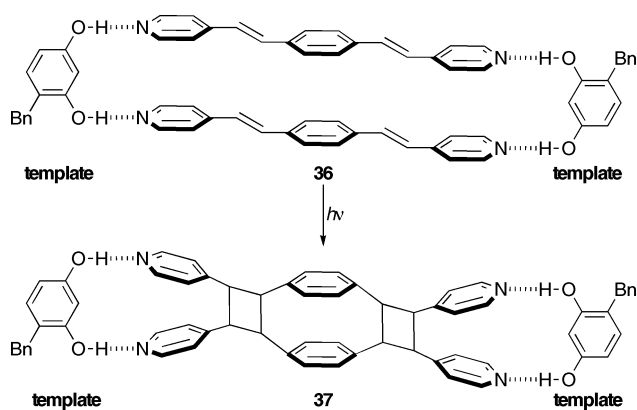
It is becoming clear that the synthesis of highly functionalised [2.2]paracyclophane-like compounds is a productive avenue of research. Recently, Fürstner has prepared hexasubstituted *N*-heterocyclic carbene cyclophane ligands and shown that the electronics of the lower ring have a profound effect on the donor ability of the carbene of the upper ring.<sup>40</sup> This could have important consequences for the 'fine-tuning' of such catalysts in a host of reactions. The current synthesis of such compounds is quite convoluted and still requires a resolution step. A more ambitious approach to highly functionalised [2.2]paracyclophanes would be *via* a *de novo* synthesis in which the functionalised cyclophane system is formed *enantioselectively*. It is conceivable that by 'templating' the ring formation or contraction step that single enantiomers could be prepared (Scheme 10); recently, there has been progress in the use of hydrogen bond complexes to engender enantioselective radical processes *via* templating.<sup>41</sup>



**Scheme 10** Potential 'templated' cyclisation.

Whilst such a strategy might appear implausible, the first steps have already been undertaken. MacGillivray has shown that [2.2]paracyclophanes **37** can be prepared by the [2 + 2] photodimerisation of the templated alkenes **36** (Scheme 11).<sup>42</sup> The reaction occurs in the solid state and occurs with 100% conversion and can be used to produce gram quantities of **37**. Whilst the current methodology does not produce chiral [2.2]paracyclophane derivatives it is an excellent foundation for further study.





**Scheme 11** 'Templated' synthesis of [2.2]paracyclophane.

To the best of our knowledge, all current routes to enantiomerically pure [2.2]paracyclophanes are based on the resolution of either an intermediate or the final product. Whilst it will be a challenge, it should be possible to apply current asymmetric technology to the development of a non-resolution based synthesis.

## Outlook

Over 50 years after their discovery, [2.2]paracyclophane and its derivatives have still to realise their full potential. Arguably, the impediment to furthering this field is the lack of attractive methods for the preparation of enantiomerically pure derivatives. Hopefully, this article has highlighted a number of approaches that could ameliorate this shortcoming. We have laid the foundations for a strategy that will permit the synthesis of a wide range of [2.2]paracyclophane derivatives from common sulfoxide precursors. Whilst it is clear that present methodology has limitations, it is hopefully only a matter of time before the optimum sulfoxide is found that enables us to bring this project to fruition. The article also conveys the belief that more efficient processes for the synthesis of enantiomerically pure [2.2]paracyclophane derivatives exist. Whilst these reactions will be more challenging, they will be more rewarding and could open a new chapter in [2.2]paracyclophane chemistry.

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