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# Enantiopure Planar Chiral [2.2]Paracyclophanes: Synthesis and Applications in Asymmetric Organocatalysis

**Abstract:** This short review focuses on enantiopure planar chiral [2.2]paracyclophanes (pCps), a fascinating class of molecules which possess an unusual three-dimensional core and intriguing physicochemical properties. In the first part of the review, different synthetic strategies for preparing optically active pCps are described. Although classical resolution methods based on the synthesis and separation of diastereoisomeric products still dominate the field, recent advances involving the kinetic resolution of racemic compounds and the desymmetrization of *meso* derivatives open up new possibilities to access enantiopure key intermediates on synthetically useful scales.

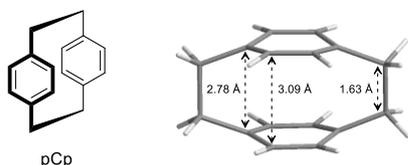
Due to their advantageous properties including high configurational and chemical stability, [2.2]paracyclophanes are increasingly employed in various research fields, ranging from stereoselective synthesis to material sciences. The applications of [2.2]paracyclophanes in asymmetric organocatalysis are described in the second part of the review. While historically enantiopure pCps have been mainly employed by organic chemists as chiral ligands in transition-metal catalysis, these compounds can also be used as efficient catalysts in metal-free reactions, and may inspire the development of new transformations in the near future.

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**Keywords:** [2.2]Paracyclophanes, planar chirality, enantioselectivity, stereoselective synthesis, asymmetric organocatalysis

## Introduction

Since its discovery in 1949 by Brown and Farthing,<sup>1</sup> [2.2]paracyclophane (pCp) has been of great interest to the scientific community due to its interesting structural and chemical properties. Constituted of two benzene rings stacked on top of each other, unable to rotate on their axis, and linked together by two ethylene bridges at their *para* positions (Figure 1), [2.2]paracyclophane is the smallest compound of the cyclophane family.<sup>2</sup> X-Ray crystallographic analysis by Trueblood *et al.* in 1972 revealed that the two co-facial phenyl ring of pCp assume an unusual boat-shaped conformation (Figure 1).<sup>3</sup> Further crystallographic and computational studies since then have extended our knowledge of the structural features, and molecular dynamics of unsubstituted [2.2]paracyclophanes.<sup>4-6</sup> At low temperature, this molecule is nowadays believed to adopt two distinct distorted geometries with a  $D_2$  symmetry. The rapid interconversion between the  $D_2$  conformers globally affords an achiral  $D_{2h}$  strained structure at room temperature.



**FIGURE 1.** Structure of unsubstituted [2.2]paracyclophane

The conformational tension of pCp impacts the conjugation of the  $\pi$ -systems, and consequently the reactivity of its aromatic units. Thus, although classical benzene chemistry (*e.g.* Friedel-Craft acylations, halogenations, or metal-catalysed cross couplings) is usually employed to decorate [2.2]paracyclophane, an array of transformations, rarely observed for more common aromatic compounds, is also allowed to take place (*i. e.* Diels-Alder cycloadditions, hydrogenations or ionic additions).<sup>7-10</sup> One of the most intriguing features of pCp is the ability of substituents

on one *deck* to modify the reactivity of the system by activating or deactivating other positions on both rings. Examples of this peculiar behaviour include the regioselective *pseudo-gem* bromination of ester, nitro, and amide derivatives,<sup>11,12</sup> as well as the Vilsmeier-Haack *para*-formylation of *N*-substituted amino compounds.<sup>13</sup>

The two aromatic units of [2.2]paracyclophane possess a total of eight possible modification sites. As soon as a substituent is introduced onto the pCp framework, planar chiral compounds are obtained (Figure 2).<sup>14</sup> In the presence of more than one functional group, complex chiral molecules can easily be formed. These derivatives are usually described by taking into account their substitution patterns as exemplified in Figure 2. In addition to *ortho*-, *meta*- and *para*-substituted substrates, showing two different functional groups on the same aromatic ring of the pCp core, *pseudo-gem*, *pseudo-ortho*, *pseudo-meta* or *pseudo-para* compounds can be obtained when the substituents are located onto the two pCp *decks*.

The first experimental evidence of the inherent chirality of functionalized pCps was brought by Cram and Allinger in 1955 through an elegant diastereoselective crystallization of the brucine salts of 4-carboxy[2.2]paracyclophane.<sup>15</sup>

In 1966, Cahn, Ingold and Prelog set up the rules to attribute the absolute configuration of enantiopure pCps.<sup>16</sup>

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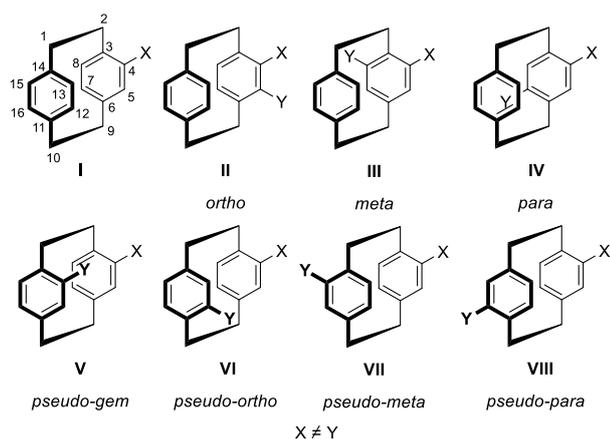


FIGURE 2. Planar chiral molecules derived from [2.2]paracyclophane

According to their proposition, one must place the most substituted ring in the furthest position (backplane) and start numbering atoms from the first out-of-plane carbon of the closest bridge (pilot atom, P) to the highest priority substituent. The  $R_p$  and  $S_p$  descriptors (p for identifying planar chirality) are nowadays commonly employed in cyclophane chemistry (Figure 3).

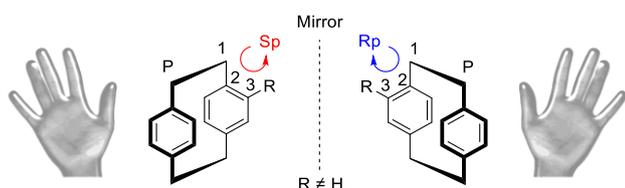


FIGURE 3. Description of the absolute configuration of pCps

Beginning in the late 1990s, organic chemists have taken advantage of the uncommon structure and reactivity of pCp to develop original planar chiral substrates that can be useful as ligands or catalysts in asymmetric synthesis.<sup>17-22</sup> Planar chiral [2.2]paracyclophanes have also been extensively employed as organic building blocks in material sciences.<sup>23-24</sup> However, obtaining enantiopure synthons to chemically design such compounds has been, and remains, quite challenging. In this up-to-date review, we will describe the different possible strategies for obtaining optically pure [2.2]paracyclophanes. We will then present the applications of these compounds in organic chemistry, with a particular focus on their use in asymmetric organocatalysis.

### Synthesis of enantiopure pCps

More than seventy years have passed since the first evidence of the chiral properties of pCps.<sup>15</sup> From that moment on, as already pointed out, different substrates bearing one or more substituents have been isolated in their enantiopure forms, and applied in various scientific fields.

In many cases, the synthesis of complex planar chiral [2.2]paracyclophanes relies on the preparation and derivatization of optically active key intermediates. To obtain such compounds, different strategies have been developed over the years. In the following part of this review, we present an overview of these techniques, which include i) chromatography purification on chiral stationary phases, ii) classical chemical resolutions involving the formation of diastereomeric products, iii) chemical or enzymatic kinetic resolutions, and iv) the desymmetrization of *meso* compounds.

### CHROMATOGRAPHY PURIFICATION ON CHIRAL STATIONARY PHASES

High performance liquid chromatography (HPLC) on chiral stationary phases is nowadays the most widely used method for determining the purity and enantiomeric excess of optically active compounds. HPLC on semi-preparative or preparative scales can also be employed as an effective way to separate the two enantiomers of racemic mixtures. Although costly, this approach has been extensively applied in paracyclophane chemistry to access a variety of enantiopure products, such as pCp-based acids,<sup>25</sup> anilines,<sup>26</sup> imines or hydrazones,<sup>27</sup> and sulfur-containing compounds<sup>28</sup> among many others.<sup>29-33</sup> Moreover, even if it is not always easy to implement, preparative chiral HPLC today remains a method of choice for the late-stage separation of complex pCp molecules.<sup>34</sup>

Despite earning less recognition as a resolution method in comparison with HPLC, gas chromatography (GC) is a valuable technique frequently employed for separating and analysing low-molecular-weight organic compounds. By using modified silica capillary columns and cyclodextrins as chiral selectors, GC has been successfully exploited in 1994 to resolve the two enantiomers of a whole range of mono-substituted pCp derivatives.<sup>35</sup> The temperature has been kept between 140 °C and 150 °C to avoid homolytic cleavage of the molecules. However, while very efficient on an analytical scale, to the best of our knowledge, GC separations of planar chiral [2.2]paracyclophanes have hardly been transferred to preparatory scale up to now.

Semi-preparative supercritical fluid chromatography (SFC) can be considered as a valuable alternative to HPLC and GC for the resolution of chiral compounds due to its higher separation speed, and the use of mobile phases that mostly evaporate during fraction collection. In spite of its benefits and high potential, SFC has rarely been used to isolate enantiopure [2.2]paracyclophanes<sup>36</sup> possibly because of the expensive equipment required to perform chiral purifications on synthetically useful scales.

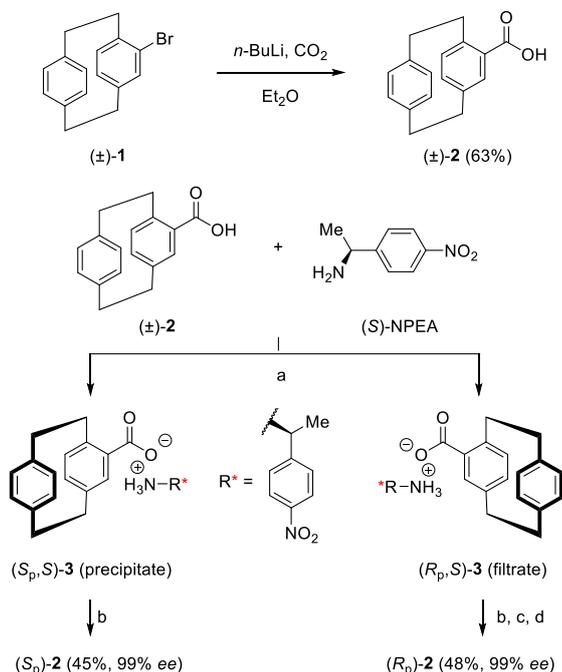
### CLASSICAL CHEMICAL RESOLUTIONS

Already employed by Pasteur more than 150 years ago,<sup>37</sup> classical resolutions are the oldest way of separating two enantiomers. These processes are based on the isolation of diastereomeric salts formed by an acid-base reaction between a racemate and an optically pure partner. Successive recrystallizations typically yield enantiopure products thanks to the different physical properties of the salts. Similarly, chemical resolutions involve reversible covalent modifications of racemic mixtures with chiral reagents. The resulting diastereomeric products can then be separated by chromatography. In both cases, an additional chemical step is required to recover the initially sought compounds in their enantiopure forms: hydrolysis of the salt in the first case, and removal of the chiral auxiliary in the second case. Despite being costly and time-consuming, classical and chemical resolutions can still be considered valuable methods for obtaining enantiopure chemicals, and are, again today, the most frequently employed techniques to access optically active pCps. In the next sections, the different approaches used to isolate planar chiral pCps will be subdivided according to the class of compounds that undergo the resolution procedure.

## Carboxylic acids

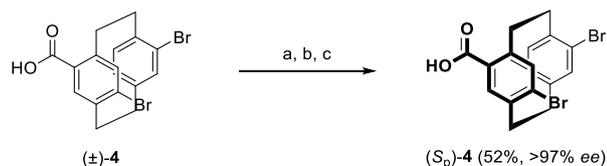
As mentioned previously, the first classical resolution of 4-carboxy[2.2]paracyclophane was described as early as 1955, when the racemic compound was resolved by successive recrystallizations of its brucine salt.<sup>15</sup>

In 1998, an improved synthesis of enantiopure 4-carboxy[2.2]paracyclophane has been reported (Scheme 1). Following this approach, a lithium/halogen exchange, and consequent CO<sub>2</sub> quench can be employed to convert commercially available 4-bromo[2.2]paracyclophane ( $\pm$ )-1 into its carboxylate analogue. The racemic acid ( $\pm$ )-2 is then resolved through a reaction with  $\alpha$ -(*p*-nitrophenyl)ethylamine (NPEA) and separation of the obtained diastereoisomeric salts by filtration ((*S<sub>p</sub>*,*S*)-3 and (*R<sub>p</sub>*,*S*)-3, Scheme 1). After hydrolysis of the salts under acidic conditions, the optically pure products (*S<sub>p</sub>*)-2 and (*R<sub>p</sub>*)-2 have been isolated in 45% and 48% yields respectively.<sup>38</sup>



**SCHEME 1.** Synthesis and classical resolution of 4-carboxy[2.2]paracyclophane

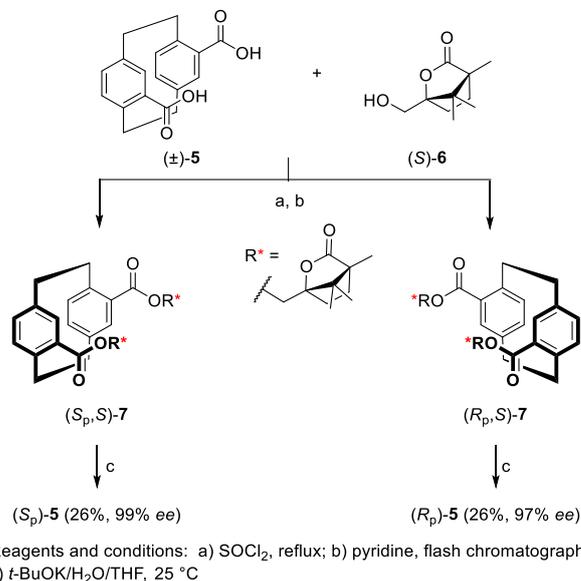
In 2004, a dibromo substituted carboxylic acid derived from pCp (( $\pm$ )-4) has been resolved using (–)-cinchonidine to selectively isolate the *S<sub>p</sub>* enantiomer in 52% yield and 97% ee after recrystallization from ethanol and hydrolysis of the salt (Scheme 2).<sup>39</sup>



**SCHEME 2.** Resolution of a dibromo substituted carboxylic acid derived from pCp

A chemical resolution of 4,12-dicarboxy[2.2]paracyclophane has been described in 2005.<sup>40</sup> In this case, the racemic compound

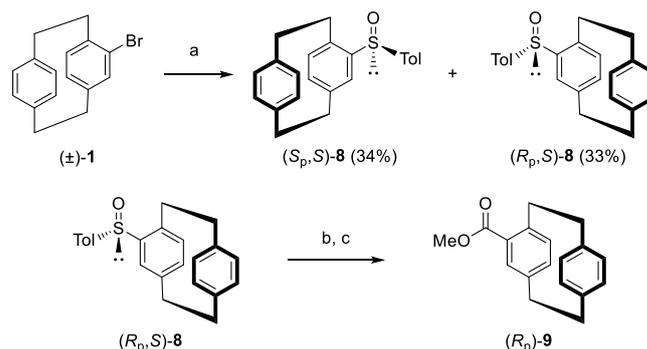
( $\pm$ )-5 is first treated with thionyl chloride, and then reacted with a chiral primary alcohol derived from (1*S*)-(–)-camphanic acid ((*S*)-6, Scheme 3). After the separation of the diastereoisomeric esters (*S<sub>p</sub>*,*S*)-7 and (*R<sub>p</sub>*,*S*)-7 by column chromatography and subsequent hydrolysis, acids (*S<sub>p</sub>*)-5 and (*R<sub>p</sub>*)-5 have been isolated with 99% and 97% ees respectively (Scheme 3).



**SCHEME 3.** Resolution of 4,12-dicarboxy[2.2]paracyclophane ( $\pm$ )-5

## Aromatic halides

Halogenated aromatic compounds are very precious reactants in organic synthesis as they offer an entry way for simple chemical modifications, notably through reactions with alkyl lithium reagents and electrophiles. This type of process has been exploited in paracyclophane chemistry to resolve racemic compounds incorporating one or more bromine atoms by introducing chiral tolyl sulfoxide moieties onto the pCp scaffold. For example, in 1991, 4-bromo[2.2]paracyclophane ( $\pm$ )-1 has been submitted to a reaction with *n*-BuLi and (–)-menthyl (–)-(*S*)-*p*-toluenesulfonate.<sup>41</sup>

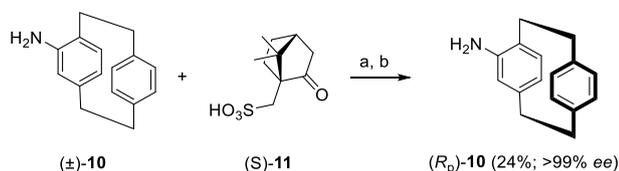


**SCHEME 4.** Resolution of 4-bromo[2.2]paracyclophane

Separation of the diastereoisomeric products by silica gel column chromatography, and treatment of the pure compounds with *n*-BuLi, CO<sub>2</sub> and diazomethane led to the formation of enantioenriched methyl esters (Scheme 4). A similar strategy has been used in 2010<sup>42</sup> and 2012<sup>43</sup> to isolate a variety of planar chiral compounds, including aldehydes, alcohols, carboxylic acids, anilines and sulfoxides.

## Anilines

The two enantiomers of 4-amino[2.2]paracyclophane ( $\pm$ )-**10** have been separated for the first time in 1997 using (S)-(+)-camphorsulfonic acid as the chiral resolving agent. Fractional crystallization of the obtained diastereoisomeric salts leads to enantiopure compound ( $R_p$ )-**10** after treatment with sodium hydroxide (0.1 M aqueous solution, Scheme 5). Starting from product ( $R_p$ )-**10** a series of transformations can be easily carried out to access a variety of planar chiral compounds.<sup>44</sup>



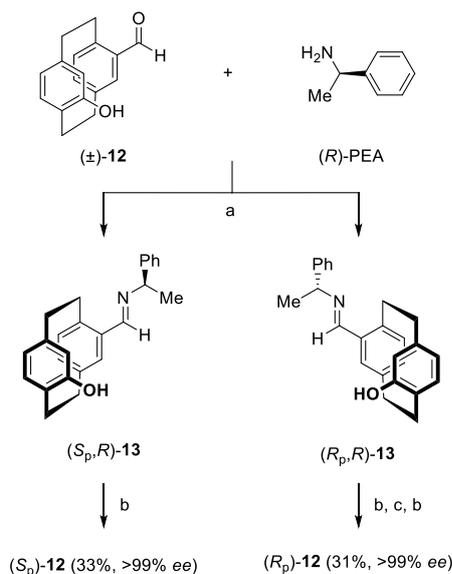
Reagents and conditions: a) EtOAc, 0 °C, 48 h then filtration; b) NaOH<sub>aq</sub> (0.1 M)

**SCHEME 5.** Resolution of 4-amino[2.2]paracyclophane

## Aldehydes and ketones

Because of their chemical versatility, carbonyl derivatives are commonly employed as intermediates in organic synthesis. Aldehydes and ketones derived from [2.2]paracyclophane are no exception to that rule. Indeed, over the years, these compounds have repeatedly proved to be valuable precursors of complex pCp molecules both in their racemic and enantiopure forms.

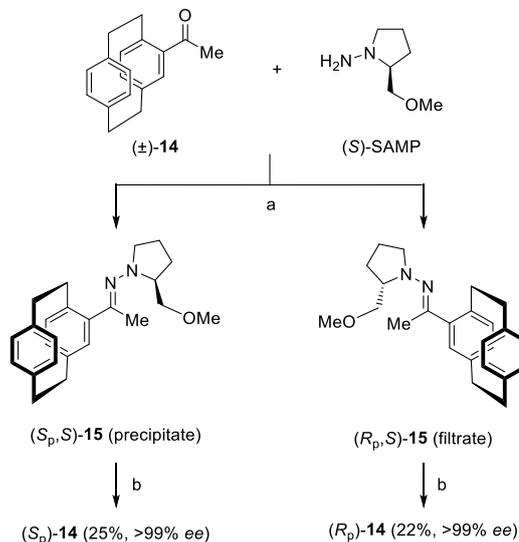
Chemical resolutions of formylated or acetylated pCps bearing different substituents have mainly been carried out by using ( $R$ )- or ( $S$ )- $\alpha$ -phenylethylamine (PEA) as chiral reagents.<sup>45-52</sup> For example, 4-formyl-5-hydroxy[2.2]paracyclophane ( $\pm$ )-**12** readily reacts with ( $R$ )-PEA to form two diastereoisomeric imines that can be separated by recrystallization in MeOH. After acid hydrolysis, the enantiopure product ( $S_p$ )-**12** has been isolated in 33% yield (Scheme 6). Partially resolved aldehyde ( $R_p$ )-**12**, on its side, needs to be submitted to a second resolution cycle, this time in the presence of ( $S$ )-PEA, to access the enantiopure isomer ( $R_p$ )-**12** in 31% overall yield (Scheme 6).<sup>51</sup>



Reagents and conditions: a) Benzene, 4Å molecular sieves, 80 °C, 13 h, then crystallization from MeOH; b) HCl (2 M aqueous solution), MeOH,  $\Delta$ , 3 h; c) ( $S$ )-PEA, benzene, 4Å molecular sieves, 80 °C, 13 h, then crystallization from MeOH.

**SCHEME 6.** Resolution of 4-formyl-5-hydroxy-[2.2]paracyclophane

In addition to the reactions with PEA, 4-acetyl[2.2]paracyclophane ( $\pm$ )-**14** can be resolved using ( $S$ )-(-)-SAMP (Ender's chiral auxiliary).<sup>53</sup> After the separation and hydrolysis of the diastereoisomeric hydrazones ( $S_p,S$ )-**15** and ( $R_p,S$ )-**15**, the two enantiomers of ketone **14** could be isolated in 22-25% yields and >99% ee.

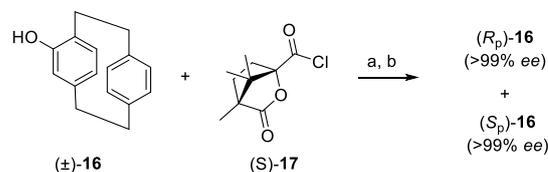


Reagents and conditions: a)  $p$ -TsOH, benzene,  $\Delta$ , 19 h; b) oxalic acid.

**SCHEME 7.** Resolution of 4-acetyl-12-hydroxy[2.2]paracyclophane

## Phenols

Enantiopure mono- and di-hydroxy-substituted pCps can be obtained through the separation of diastereoisomeric ester adducts formed upon treatment with activated camphanoyl derivatives.<sup>54-60</sup> This quite general approach can be exemplified by the chemical resolution of 4-hydroxy[2.2]paracyclophane ( $\pm$ )-**16**.<sup>57</sup> This compound has been submitted to a reaction with (1*S*)-(-)-camphanoyl chloride (( $S$ )-**17**, Scheme 8) to form a couple of diastereoisomers which can be easily separated by silica gel column chromatography (Scheme 8). After saponification with KOH in MeOH, products ( $S_p$ )-**16** and ( $R_p$ )-**16** have both been obtained in up to 38% yield and >99% ee (Scheme 8).



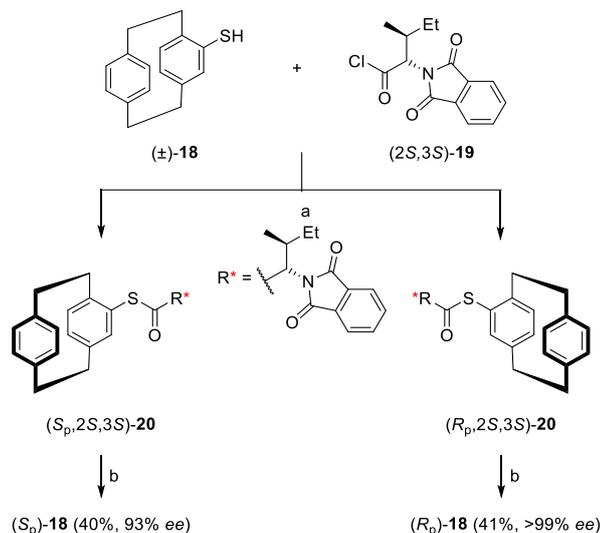
Reagents and conditions: a) Py, 20 °C, 6 h, then crystallization (EtOAc), and flash chromatography; b) KOH, MeOH, -20 °C, 2 h

**SCHEME 8.** Resolution of 4-hydroxy[2.2]paracyclophane

## Thiols

In 2016, an interesting classical resolution of [2.2]paracyclophane-4-thiol ( $\pm$ )-**18** has been described.<sup>61</sup> Based on the screening of a wide range of chiral auxiliaries, activated  $L$ -isoleucine (( $2S,3S$ )-**19**, Scheme 9) appears to be the reagent of choice to access enantioenriched thiols ( $S_p$ )-**18** and ( $R_p$ )-**18** through the formation of diastereoisomeric salts. Indeed, after the synthesis, separation, and hydrolysis of compounds ( $S_p,2S,3S$ )-**20** and ( $R_p,2S,3S$ )-**20**, products ( $S_p$ )-**18** and ( $R_p$ )-**18**

could be obtained in approximately 40% yield, with 93% and >99% *ees* respectively (Scheme 9). This procedure appears to be quite appealing as the resolution can be run on a large scale without any loss in efficiency.

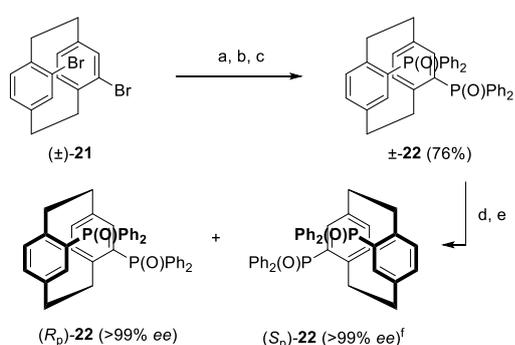


Reagents and conditions: a) DCM, Et<sub>3</sub>N, rt, 48 h, then crystallization and flash chromatography; b) LiAlH<sub>4</sub>, THF, -78 °C to rt, 24 h

**SCHEME 9.** Classical resolution of 4-thiol[2.2]paracyclophane

### Phosphine oxides

Starting from commercially available 4,12-dibromo[2.2]paracyclophane (±)-**21** a double lithium-halogen exchange, followed by transmetalation with magnesium, and subsequent reaction with diphenylphosphinic chloride leads to the formation of phosphine oxide (±)-**22**.<sup>62</sup> This compound can be resolved with dibenzoyl-*D*-tartaric acid as described in Scheme 10.



Reagents and conditions: a) *t*-BuLi, THF, Ar, -80 °C; b) MgBr·Et<sub>2</sub>O, 10 °C, 45 min; c) Diphenylphosphinyl chloride, 10 °C to 35 °C, 10 min; d) (+)-dibenzoyl-*D*-tartaric acid, CHCl<sub>3</sub>, 60 °C; e) NaOH (0.5 M aq. solution), rt; f) High enantiomeric excess is obtained after a second resolution cycle with (-)-dibenzoyl-*L*-tartaric acid.

**SCHEME 10.** Synthesis and classical resolution of pCp-based phosphine oxides

The resulting enantiopure products have been used as key intermediates in one of the first syntheses of PhanePhos, a well-known pCp-based planar chiral ligand (*vide infra*). Various substituents can be introduced onto the phosphorous atoms simply by using different diarylphosphinic chloride reagents (Ar<sub>2</sub>POCl), thus opening the pathway for the preparation of a

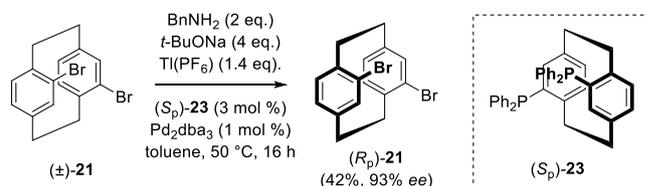
wide range of optically active products. Unsymmetrical phosphorous derivatives<sup>63</sup> and mono-substituted substrates<sup>64</sup> have been prepared as well following this synthetic strategy.

### CHEMICAL OR ENZYMATIC KINETIC RESOLUTIONS

Among many classes of asymmetric reactions, kinetic resolutions (KR) are certainly attractive tools for organic chemists. In kinetic resolutions, two enantiomers undergo a transformation in the presence of a chiral catalyst or an enzyme and react with different reaction rates. Theoretically, at 50% of conversion, one enantiomer is isolated as the reaction product; the other is recovered as starting material. KR may constitute a valuable alternative to both stoichiometric resolutions and chromatographic separations that are generally costly in terms of reagents, may be time-consuming or require pricy high-pressure equipment to deliver enantiopure material on a large scale. After an early proof-of-concept described in 1968,<sup>65</sup> kinetic resolutions have been successfully implemented in paracyclophane chemistry to access enantiopure compounds showing different reactive functions. In the next section of this review, the diverse methods developed so far will be described by ordering them according to the nature of the pCp derivatives submitted to the KR processes.

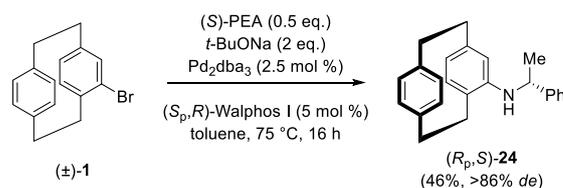
#### Aromatic halides

Enantioenriched 4,12-dibromo[2.2]paracyclophane (*R<sub>p</sub>*)-**21** has been obtained in 1997 through a kinetic resolution process based on a palladium-catalysed Buchwald-Hartwig coupling (Scheme 11).<sup>66</sup> Interestingly, PhanePhos (*S<sub>p</sub>*)-**23** has been identified as the best chiral ligand to perform this transformation. Indeed, after 16 h of reaction at 50 °C, compound (*R<sub>p</sub>*)-**21** could be isolated in 42% yield and 93% *ee* together with small amounts of mono- and di-substituted pCp-based amines.



**SCHEME 11.** Kinetic resolution of 4,12-dibromo[2.2]paracyclophane via Buchwald-Hartwig coupling

More recently, a diastereoselective Buchwald-Hartwig coupling between 4-bromo[2.2]paracyclophane (±)-**1** and (*S*)-PEA has been reported to proceed smoothly in the presence of Pd<sub>2</sub>(dba)<sub>3</sub>, and chiral ligands. Using 0.5 equivalents of amine and (*S<sub>p</sub>,R*)-Walphos I as chiral ligand, a kinetic resolution of compound (±)-**1** has been carried out to isolate the aminated product (*R<sub>p</sub>,S*)-**24** in 46% yield and 86% *de* (Scheme 12). Unreacted enantioenriched derivative (*S<sub>p</sub>*)-**1** could also be recovered after the reaction.<sup>67</sup>

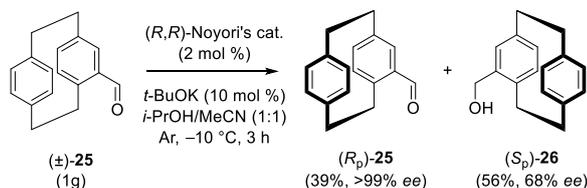


**SCHEME 12.** Kinetic resolution of 4-bromo[2.2]paracyclophane via Buchwald-Hartwig coupling

## Aldehydes and ketones

In addition to the stoichiometric resolution methods described above, aldehydes and ketones derived from [2.2]paracyclophane can be obtained in their enantiopure form using different kinetic resolution approaches.

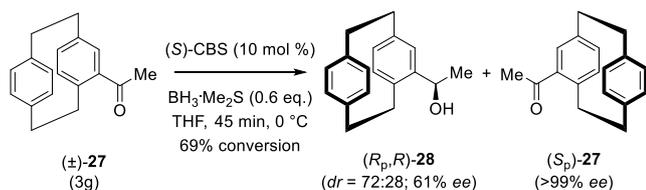
Optically active 4-formyl[2.2]paracyclophane can easily be prepared on synthetically useful scales through asymmetric transfer hydrogenation.<sup>68</sup> Indeed, when the racemic compound ( $\pm$ )-**25** is treated with  $\text{RuCl}(\text{p-cymene})[(R,R)\text{-Ts-DPEN}]$  (Noyori's catalyst) and  $t\text{-BuOK}$  in a 1:1  $i\text{-PrOH-MeCN}$  mixture at  $-10^\circ\text{C}$ , the unreacted aldehyde ( $R_p$ )-**25** and reduced alcohol ( $S_p$ )-**26** can be resolved to 99% ee and 68% ee respectively at 56% conversion (Scheme 13). *Pseudo-gem* and *pseudo-para* bromo-substituted pCp-based aldehydes can be obtained as well in high yields and enantioselectivities following this efficient strategy.<sup>69</sup>



**SCHEME 13.** Kinetic resolution of 4-formyl[2.2]paracyclophane

4-Formyl[2.2]paracyclophane ( $\pm$ )-**25** has also been kinetically resolved using a yeast strain (DSM 11285) to reduce the carbonyl group. Nonetheless, in this case, a high volume of culture medium ( $\sim 2\text{ L}$ ) is required to convert small quantities of starting material (80 mg), and only few milligrams of enantiopure products can be obtained.<sup>70</sup>

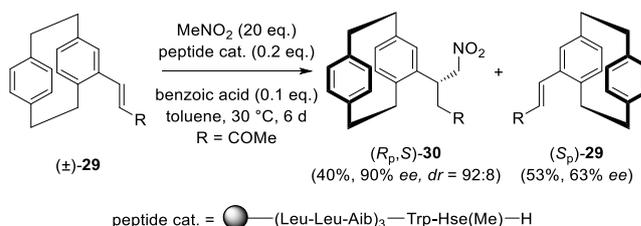
The kinetic resolution of 4-acetyl[2.2]paracyclophane ( $\pm$ )-**27** can also be performed through catalytic asymmetric reductions. For example, methyl ketone ( $S_p$ )-**27** and benzylic alcohol ( $R_p,R$ )-**28** have been isolated in good yields, with >99% and 61% ees respectively, using borane as the reducing agent together with commercially available Corey-Bakshi-Shibata oxazaborolidine catalyst (( $S$ )-CBS, Scheme 14).<sup>71</sup>



**SCHEME 14.** Kinetic resolution of 4-acetyl[2.2]paracyclophane

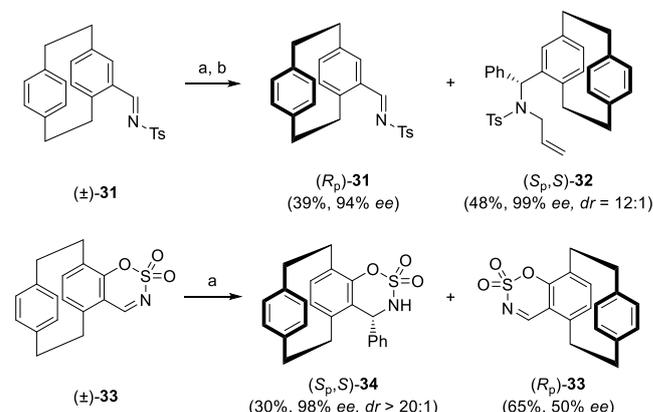
Very recently, 4-acetyl[2.2]paracyclophane ( $\pm$ )-**27** has been efficiently resolved on a synthetically useful scale by asymmetric hydrogenation in the presence of a ruthenium-based catalyst (( $S$ )-RUCY<sup>®</sup>-XylBINAP). High hydrogen pressures are, however, required for the reaction to work.<sup>72</sup>

$\alpha,\beta$ -Unsaturated ketones can be submitted to kinetic resolution as well.<sup>73</sup> Starting from racemic pCp ( $\pm$ )-**29**, Michael addition of nitromethane promoted by a chiral helical peptide affords nitromethylated product ( $R_p,S$ )-**30** in 40% yield and 90% ee after 6 d at  $30^\circ\text{C}$ . Unreacted compound ( $S_p$ )-**29** is recovered as well after the reaction in 53% yield and 63% ee (Scheme 15).



**SCHEME 15.** Kinetic resolution of pCp-based  $\alpha,\beta$ -unsaturated methyl ketone  
**Imines and *N*-sulfonylimines**

Very recently, palladium-catalysed Suzuki couplings have been successfully exploited to perform the kinetic resolution of imines<sup>74</sup> and cyclic *N*-sulfonylimines.<sup>75</sup> Following these procedures, the racemic pCp-based derivatives ( $\pm$ )-**31** and ( $\pm$ )-**33** are submitted to a reaction with various aryl-boronic acids,  $\text{Pd}(\text{TFA})_2$ , and a planar chiral ferrocene-derived phosphinoxazoline ligand. At approximately 50% conversion, one of the enantiomers is recovered as unreacted starting material in up to 99% ee, while the other enantiomer is isolated as an arylated product in high  $dr$  and  $er$  (up to 20:1, and 99:1 respectively).

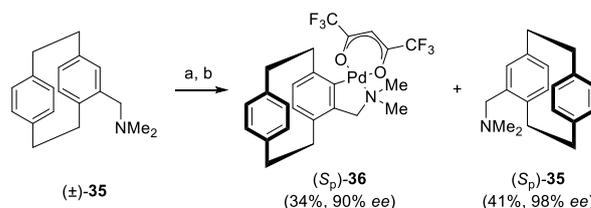


Reagents and conditions: a)  $\text{PhB}(\text{OH})_2$  (1 eq.),  $\text{Pd}(\text{TFA})_2$  (5.0 mol%), ferrocene ligand (5.0 mol%), TFE,  $60^\circ\text{C}$ , 12/15 h; b) allyl bromide (1 eq.),  $\text{NaH}$  (1.3 eq.), DMF,  $0^\circ\text{C}$  to rt, 2 h.

**SCHEME 16.** Examples of kinetic resolution of pCp-based imines and cyclic *N*-sulfonylimines

## Amines

The synthesis of palladacycles has elegantly been applied in paracyclophane chemistry to realize the kinetic resolution of *N,N*-dimethylaminomethyl[2.2]paracyclophane.<sup>76,77</sup>



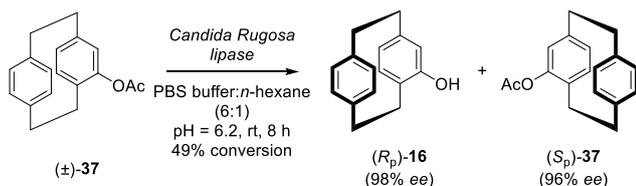
Reagents and conditions: a)  $\text{Na}_2\text{PdCl}_4$  (1 eq.), (*R*)-*N*-acetylphenylalanine (1 eq.),  $\text{MeOH}/\text{H}_2\text{O}/\text{DCM}$ , pH 8.2, rt, 48 h; b)  $\text{Na}(\text{hfacac})$ ,  $\text{H}_2\text{O}/\text{acetone}$ , rt.

**SCHEME 17.** Kinetic resolution of *N,N*-dimethylaminomethyl[2.2]paracyclophane

When reacted with (*R*)-*N*-acetylphenylalanine and Pd(II) salts, the racemic substrate ( $\pm$ )-**35** affords the metalated product (*S<sub>p</sub>*)-**36** in 34% yield and 90% *ee*, together with unreacted compound (*S<sub>p</sub>*)-**35**, which can be obtained in 41% yield and 98% *ee* (Scheme 17). While amine (*S<sub>p</sub>*)-**35** can serve as a precursor of more complex pCp derivatives, the enantioenriched pCp-based palladacycle may be useful as catalyst to promote asymmetric transformations.

## Esters

Enzymes have frequently been exploited by organic chemists as biocatalysts to resolve synthetically useful compounds since they usually induce high levels of enantioselection and are environmentally friendly. Together with oxidoreductases, lipases are possibly the most frequently used enzymes in asymmetric catalysis. Among many other substrates, these biomolecules can catalyse the kinetic resolution of 4-acetoxy[2.2]paracyclophane ( $\pm$ )-**37**.<sup>78-80</sup> In the presence of commercially available *Candida rugosa* lipase (CRL) optically active 4-hydroxy[2.2]paracyclophane (*R<sub>p</sub>*)-**16** has indeed been obtained in 47% yield and 96% *ee* through ester hydrolysis. Unreacted derivative (*S<sub>p</sub>*)-**37** has been recovered as well in high yield and selectivity (Scheme 18).<sup>81</sup> The same enzyme can be employed to access enantiopure 4,12-dihydroxy[2.2]paracyclophane through similar biotransformations.<sup>82</sup>



**SCHEME 18.** Enzymatic kinetic resolution of 4-hydroxy[2.2]paracyclophane

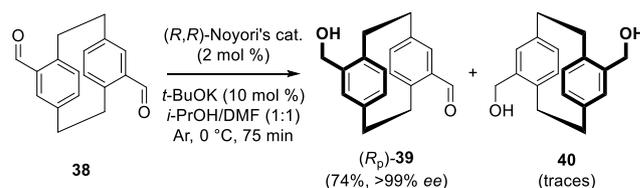
## DESYMMETRIZATIONS

As a logical consequence of separating racemic mixtures, one of the main limitations of all resolution methods, unrelated to how efficient they are, is their maximum theoretical yield of 50%. The desymmetrization of *meso* compounds, on the other hand, can theoretically afford enantiopure products in up to 100% yield. This technique, which relies on the differentiation of the prochiral sites of achiral molecules, has widely been exploited in stereoselective synthesis, but rarely applied to [2.2]paracyclophanes.

### Aldehyde derivatives

The desymmetrization of achiral *meso* compounds derived from pCp has been described recently. Noyori asymmetric transfer hydrogenations under the conditions previously employed to perform the kinetic resolution of racemic 4-formyl[2.2]paracyclophane can afford enantioenriched products in high yields and selectivities starting from centrosymmetric dialdehydes. In fact, when using *t*-BuOK as a base and RuCl(*p*-cymene)[(*R,R*)-Ts-DPEN] as the catalyst in a 1:1 *i*-PrOH/DMF mixture at 0 °C, 4,16-diformyl[2.2]paracyclophane is reduced smoothly to afford the product (*R<sub>p</sub>*)-**39** in 74% yield and >99% *ee* (Scheme 19). Interestingly, only small amounts of diol **40** have been isolated after the reaction.<sup>83</sup> Bromine atoms can be introduced *para* to the aldehyde groups to obtain optically active

tetra-substituted compounds in a rapid and efficient fashion following this convenient strategy.<sup>69</sup>



**SCHEME 19.** Desymmetrization of 4,16-diformyl[2.2]paracyclophane

## Applications

As mentioned above, the chirality of [2.2]paracyclophanes was reported by Cram and Allinger as early as 1955.<sup>15</sup> At first, nearly all stereochemical studies involving planar chiral pCps focused on the synthesis of mono-substituted derivatives and the determination of their absolute configuration. Because of their advantageous properties, such as a high configurational stability (200 °C), good tolerance to the action of acids and bases, chemical stability towards light or oxidants, and ease of handling, from the early 1990s onward, chiral paracyclophanes have gradually emerged as powerful ligands or catalysts in asymmetric synthesis, and several poly-substituted compounds have been prepared. Nowadays, enantiopure paracyclophanes are increasingly employed as precursors for the development of materials with original chiroptical behaviours. The synthesis of planar chiral pCp ligands and their use in enantioselective metal-catalysed reactions have been extensively reviewed.<sup>17-22</sup> Reviews on the preparation and properties of optically active materials derived from [2.2]paracyclophane have also appeared in recent years.<sup>23-24</sup> In the next sections, we will therefore mainly focus our attention on the recent applications of pCps in the field of asymmetric organocatalysis.<sup>84</sup>

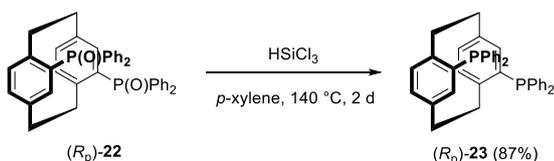
### PLANAR-CHIRAL PCP-BASED ORGANOCATALYSTS

A variety of planar-chiral organocatalysts derived from [2.2]paracyclophane have been synthesized over the last three decades. These compounds have been successfully employed to promote different types of asymmetric transformations with various degrees of selectivity. In the following part of this review, the pCp-based organocatalysts will be subdivided into several classes according to the nature of their reactive functions. The synthesis of these compounds will be described below, together with representative examples of their use in various metal-free reactions.

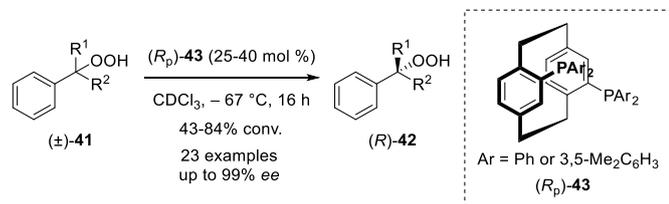
### Phosphines

PhanePhos is without doubt the most well-known *C*<sub>2</sub>-symmetrical diphosphine derived from [2.2]paracyclophane. First synthesized in an industrial laboratory in 1997,<sup>62</sup> this compound is nowadays commercially available through major chemical suppliers. PhanePhos can be prepared starting from enantiopure phosphine oxide (*R<sub>p</sub>*)-**22** through a reduction with trichlorosilane (Scheme 20).

In addition to their role as ligands in metal catalysis,<sup>19</sup> enantiopure PhanePhos and its derivatives have been employed as stoichiometric reductants to promote the kinetic resolution of hydroperoxides. In particular, the sterically hindered compound (*R<sub>p</sub>*)-**43** provides high enantioselectivities in this transformation (up to 99% *ee*, Scheme 21).<sup>85</sup>

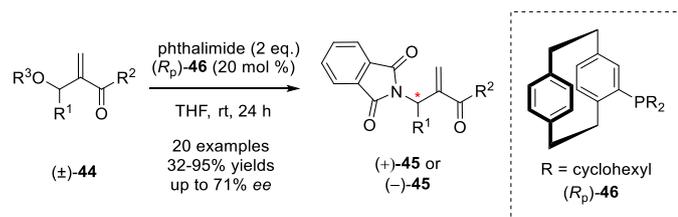


**SCHEME 20.** Synthetic pathway for the preparation of PhanePhos and its derivatives



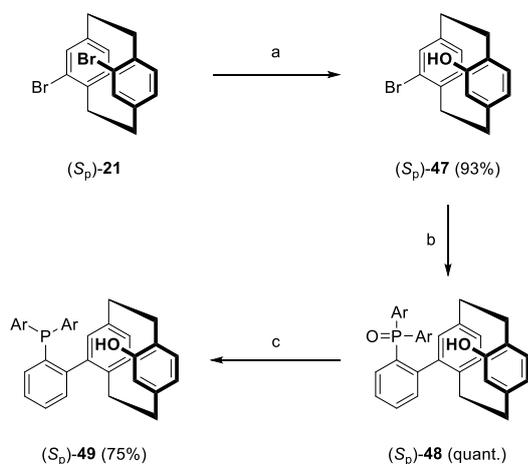
**SCHEME 21.** Kinetic resolution of hydroperoxides

pCp-Based monophosphines obtained starting from enantiopure mono-substituted phosphine oxides proved to be effective organocatalysts in asymmetric allylic substitution reactions. The direct functionalization of Morita–Baylis–Hillman products have indeed been achieved with good degrees of enantioselectivity (up to 71% ee) in the presence of pCps derivatives carrying aliphatic substituents on their phosphorous atom (e.g.  $(R_p)$ -46, Scheme 22).<sup>86</sup>



**SCHEME 22.** Enantioselective allylic substitution reactions

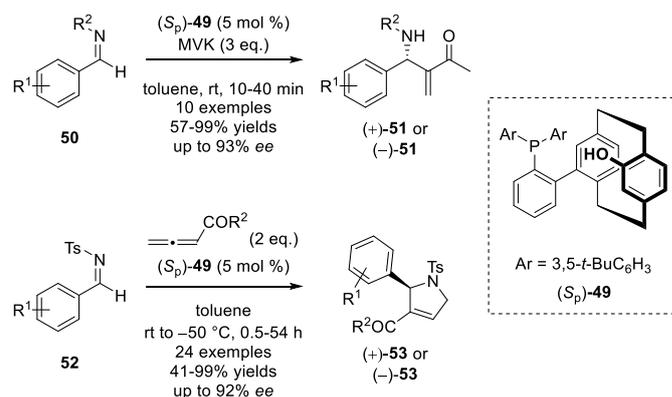
In addition to PhanePhos and its derivatives, planar chiral pCp-based bifunctional phosphine-phenol compounds have been prepared and used as catalysts in metal-free reactions (Scheme 23).<sup>87-90</sup>



Reagents and conditions: a) *n*-BuLi, THF,  $-78$  °C, then  $B(OMe)_3$ ,  $H_2O_2$ , NaOH; b) phosphinylboronic esters,  $PdCl_2(PPh_3)_2$ ,  $Na_2CO_3$ , DMSO/ $H_2O$ ,  $100$  °C 3 h; c)  $HSiCl_3$ ,  $PhNMe_2$ , toluene,  $110$  °C, 12 h. Yields are given for Ar = Ph

**SCHEME 23.** Synthesis of planar chiral pCp-based bifunctional phosphine-phenol catalysts

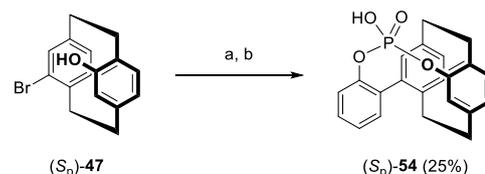
To access these compounds, 4-bromo-12-hydroxy[2.2]paracyclophane ( $S_p$ )-47 is first isolated through a mono metalation of enantiomerically pure 4,12-dibromo[2.2]-paracyclophane ( $S_p$ )-21, followed by a reaction with trimethylborate, and oxidation of the resulting product with hydrogen peroxide and sodium hydroxide. The obtained key intermediate ( $S_p$ )-47 is then engaged into a Suzuki–Miyaura coupling in the presence of phosphinylboronic esters. Subsequent reduction of the phosphine oxide group finally leads to the expected products ( $S_p$ )-49 in good overall yields (Scheme 23). Different bifunctional phosphine-phenol catalysts can also be prepared by submitting 4-bromo-12-hydroxy[2.2]paracyclophane ( $S_p$ )-47 to triflation, followed by stepwise successive Pd-catalysed cross-coupling reactions.<sup>88</sup> Bifunctional phosphine-phenol pCp derivatives such as compound ( $S_p$ )-49 have been employed to catalyse asymmetric aza-Morita-Baylis-Hillman reactions of aldimines with vinyl ketones (Scheme 24).<sup>89-90</sup> The same catalysts can also be used to promote enantioselective [3+2] annulations of unsubstituted allenic esters and *N*-tosylimines (Scheme 24).<sup>87</sup> In both transformations, bifunctional pCps provide better yields and enantioselectivities in comparison with PhanePhos or other planar chiral ligands.



**SCHEME 24.** Asymmetric transformations promoted by bifunctional phosphine-phenol pCp catalysts

### Phosphoric acids

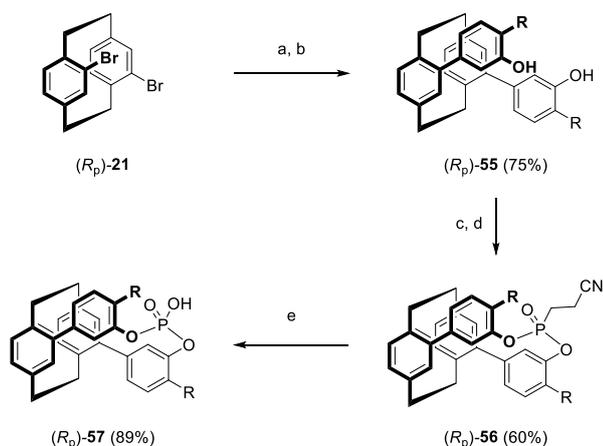
Only few examples of planar chiral phosphoric acids derived from [2.2]paracyclophane have been reported in the literature to date. Starting from enantiopure 4-bromo-12-hydroxy[2.2]paracyclophane ( $S_p$ )-47, a first pCp-based phosphoric acid has been prepared in 2012 through a Suzuki coupling, and consequent reaction with phosphoryl chloride (Scheme 25).<sup>91</sup>



Reagents and conditions: a) 2-hydroxyphenylboronic acid,  $Pd(PPh_3)_4$ ,  $Na_2CO_3(aq.)$ , DMF,  $100$  °C, 48 h; b)  $POCl_3$ , pyridine, rt, 24 h; then  $H_2O$ , rt, 24 h.

**SCHEME 25.** First synthesis of a pCp-based phosphoric acid

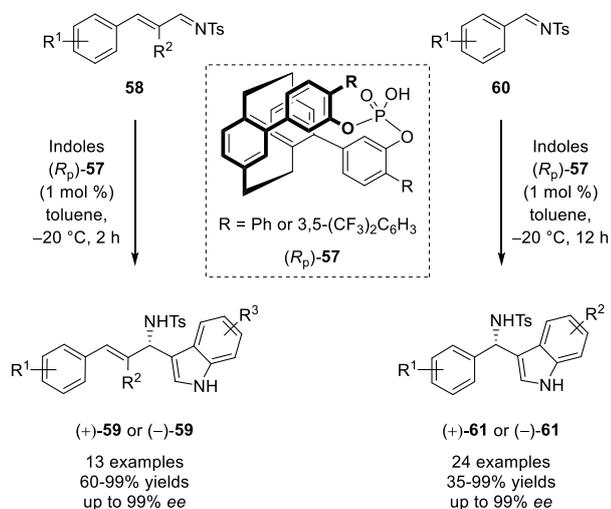
More recently, a different family of phosphoric acid derivatives showing a pCp core has been obtained in four steps using enantiopure 4,12-dibromo-[2,2]-paracyclophane ( $R_p$ )-**21** as a key precursor.<sup>92</sup> The synthetic procedure employed to access these compounds starts with a double Suzuki coupling which occurs in the presence of arylboron reagents featuring a Me-protected hydroxyl function at their meta position, and different substituents in *para* position. Demethylation with  $\text{BBr}_3$  affords [2,2]paracyclophane-based bisphenol intermediates ( $R_p$ )-**55**, which can be converted to the corresponding phosphoric acids through a cyclization with bis(diisopropylamino)(2-cyanoethoxy)phosphine, and subsequent oxidation of the resulting phosphites with tert-butyl hydroperoxide. Removal of the cyanoethyl substituent of phosphates ( $R_p$ )-**56** under basic conditions finally gives access to the desired products ( $R_p$ )-**57** (Scheme 26).



Reagents and conditions: a) aryl boronic esters,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{DMSO}/\text{H}_2\text{O}$  (10:1), 90 °C; b)  $\text{BBr}_3$ , DCM, rt; c) bis(diisopropylamino)(2-cyanoethoxy)phosphine, 1H-tetrazole, DCM; d) *t*-BuOOH, DCM; e) DBU, DCM. Yields are given for R = Me

**SCHEME 26.** Access to a different family of pCp-based phosphoric acid derivatives

The pCp-based planar chiral phosphoric acids have been employed to promote the synthesis of enantiopure 3-indolylmethanamine derivatives through asymmetric aza-Friedel-Crafts reactions (Scheme 27).<sup>91-92</sup>



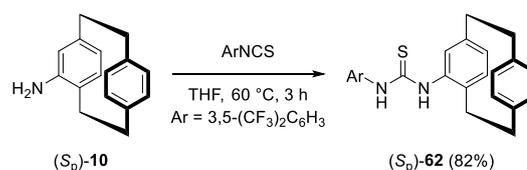
**SCHEME 27.** Asymmetric aza-Friedel-Crafts reaction

High selectivities (up to 99% ee) have been achieved in the presence of catalysts ( $R_p$ )-**57** (Scheme 27). These compounds show superior catalytic activities compared to other planar chiral Brønsted acids, including derivative ( $S_p$ )-**54**.

### Thioureas

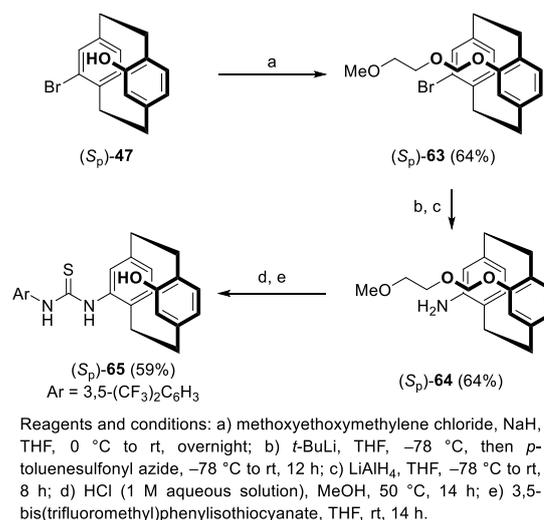
A few planar-chiral hydrogen-bond catalysts have been described in recent years. The great majority of these compounds feature either one or two thiourea groups onto the aromatic rings of [2,2]paracyclophane.

Different mono-thiourea derivatives have been synthesized starting from enantiopure precursors. Unsubstituted catalysts such as ( $S_p$ )-**62** are, for example, easily prepared through the reaction of enantiopure 4-amino[2,2]paracyclophane ( $S_p$ )-**10** with activated isothiocyanates (Scheme 28).<sup>93</sup>



**SCHEME 28.** Synthesis of unsubstituted thiourea catalysts

4-Bromo-12-hydroxy[2,2]paracyclophane ( $S_p$ )-**47** can be employed as starting material to access *pseudo-ortho* hydroxy-substituted catalysts (Scheme 29).<sup>93</sup> In this case, the hydroxy group of the molecule first needs to be protected as MEM ether. A halogen-lithium exchange can then occur, and the resulting metalated pCp derivative can undergo a reaction with  $\text{TsN}_3$  to form an azido-substituted product. Reduction of this compound to the corresponding amine, deprotection of the hydroxy group, and subsequent reaction with 3,5-bis(trifluoromethyl)phenyl isothiocyanate finally afford the expected thiourea ( $S_p$ )-**65** in 24% overall yield (Scheme 29).

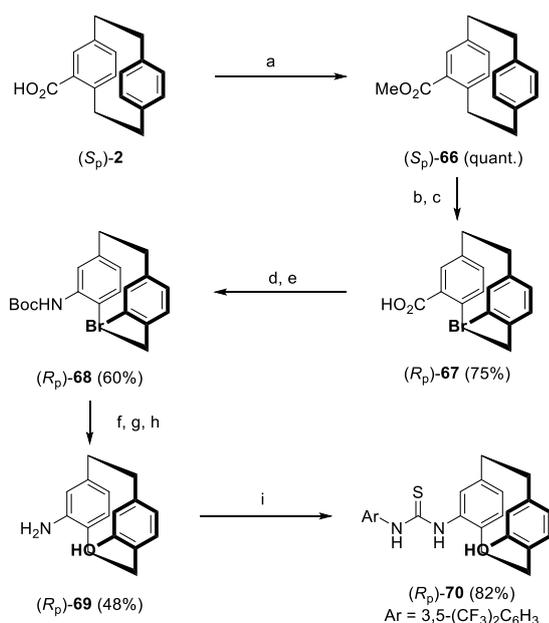


Reagents and conditions: a) methoxyethoxymethylene chloride, NaH, THF, 0 °C to rt, overnight; b) *t*-BuLi, THF, -78 °C, then *p*-toluenesulfonyl azide, -78 °C to rt, 12 h; c)  $\text{LiAlH}_4$ , THF, -78 °C to rt, 8 h; d) HCl (1 M aqueous solution), MeOH, 50 °C, 14 h; e) 3,5-bis(trifluoromethyl)phenylisothiocyanate, THF, rt, 14 h.

**SCHEME 29.** Synthesis of *pseudo-ortho* di-substituted thiourea catalysts

*Pseudo-gem* hydroxy-substituted catalysts can be prepared through the derivatization of enantiopure 4-carboxy[2,2]paracyclophane ( $S_p$ )-**2**.<sup>93</sup> Following the synthetic pathway reported in Scheme 30, this precursor is first converted to the corresponding methyl ester ( $S_p$ )-**66** through the formation of an acyl chloride, and consequent reaction with methanol. A regioselective electrophilic aromatic substitution is then

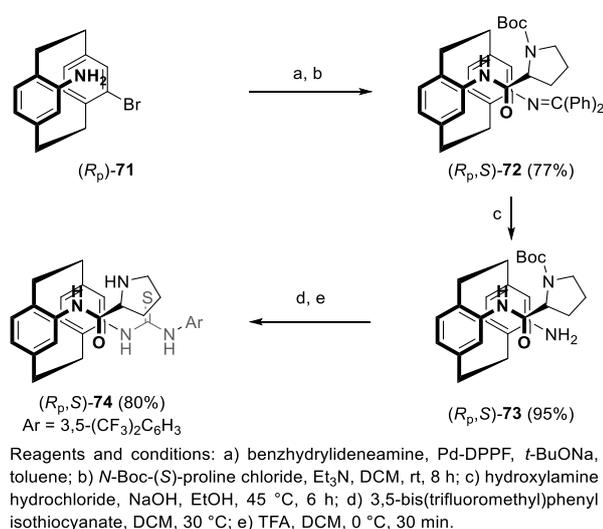
performed to functionalize the pCp framework with a bromine atom at the *pseudo-gem* position. Saponification of the resulting bromo ester affords a carboxylic acid ((*R<sub>p</sub>*)-**67**) that can be submitted to Curtius rearrangement. Boc-protected amine derivative (*R<sub>p</sub>*)-**68** is obtained by trapping the thermally generated isocyanate with *tert*-butyl alcohol. Metalation of this compound, followed by addition of trimethylborate, oxidative work-up, and removal of the protecting group with TFA leads to the formation of a substituted amino-alcohol ((*R<sub>p</sub>*)-**69**), which can react smoothly with isothiocyanates to afford various thiourea derivatives, including product (*R<sub>p</sub>*)-**70** (Scheme 30).



Reagents and conditions: a)  $\text{SOCl}_2$ , DMF, 60 °C, 12 h, then MeOH; b)  $\text{Br}_2$ ,  $\text{CCl}_4$ , Fe powder, DCM, 48 h; c) KOH, MeOH, reflux, 10 h; d)  $\text{SOCl}_2$ , DMF, 60 °C, 12 h; e)  $\text{NaN}_3$ ,  $\text{H}_2\text{O}/\text{Me}_2\text{CO}$ , 0 °C to rt, 12 h; f) toluene, *t*-BuOH, DBU, 80 °C 12 h; g) *n*-BuLi,  $\text{B}(\text{OMe})_3$ , THF, -78 °C, then  $\text{H}_2\text{O}_2/\text{NaOH}$ ; h) TFA, DCM, 40 °C, 3 h; i) 3,5-bis(trifluoromethyl)phenylisothiocyanate, THF, rt, 14 h.

**SCHEME 30.** Synthesis of *pseudo-gem* di-substituted thiourea catalysts

Chiral amino thioureas have been synthesized starting from 4-bromo-12-amino[2.2]paracyclophane (*R<sub>p</sub>*)-**71**.<sup>94</sup> The synthetic procedure leading to these compounds involve the introduction of both a benzhydrylideneamine moiety and a (*S*)-*N*-Boc-prolyl group onto the molecules through coupling reactions.

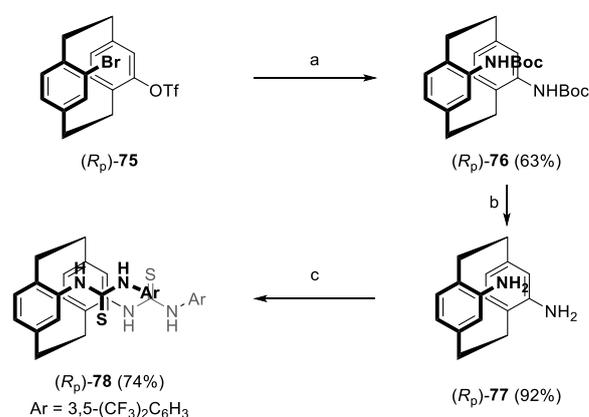


Reagents and conditions: a) benzhydrylideneamine, Pd-DPPF, *t*-BuONa, toluene; b) *N*-Boc-(*S*)-proline chloride,  $\text{Et}_3\text{N}$ , DCM, rt, 8 h; c) hydroxylamine hydrochloride, NaOH, EtOH, 45 °C, 6 h; d) 3,5-bis(trifluoromethyl)phenyl isothiocyanate, DCM, 30 °C; e) TFA, DCM, 0 °C, 30 min.

**SCHEME 31.** Synthesis of a planar chiral amino thiourea derivative

After the deprotection of the benzhydrylideneamino group under basic conditions, the thiourea motif is again introduced *via* a reaction between the free amino group and an activated isothiocyanate. Boc-deprotection with TFA finally generates the expected bifunctional product (*R<sub>p</sub>*,*S*)-**74** in 80% yield (Scheme 31).

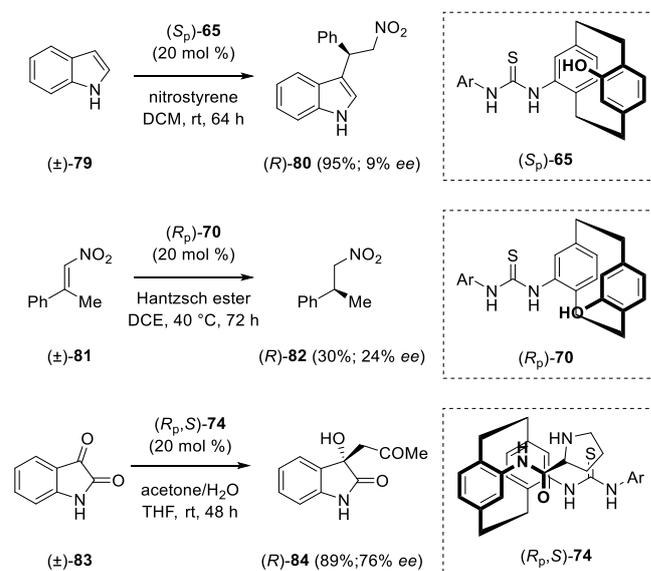
In 2013, a bis-thiourea pCp organocatalyst showing a  $\text{C}_2$  symmetry has been synthesized starting from optically pure bromo[2.2]paracyclophanyl triflate *R<sub>p</sub>*-**75** (Scheme 32).<sup>95</sup> This precursor has successfully been submitted to a double Buchwald-Hartwig coupling using *N-tert*-butyl carbamate as an ammonia equivalent in the presence of a palladium-based catalyst and JohnPhos. Subsequent removal of the Boc-protecting groups with TFA leads to the diamine key intermediate (*R<sub>p</sub>*)-**77**, which easily reacts with 3,5-bis(trifluoromethyl)phenyl isothiocyanate to afford the desired bis-thiourea derivative (*R<sub>p</sub>*)-**78** in 74% yield (Scheme 32).



Reagents and conditions: a)  $\text{BocNH}_2$ ,  $\text{Pd}_2(\text{dba})_3$ , JohnPhos, NaOPh, toluene, 85 °C, 16 h; b) TFA, DCM, rt, 1 d; c) ArNCNS, DCM, 0 °C, 1 d

**SCHEME 32.** Synthesis of a bis-thiourea pCp-based organocatalyst

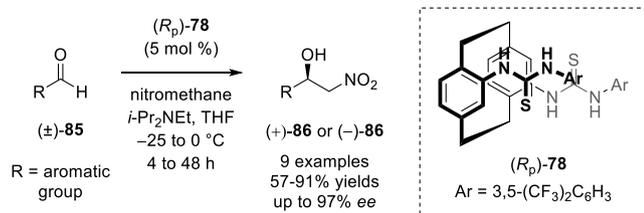
Planar-chiral hydrogen-bond catalysts incorporating a single thiourea moiety have been employed to promote enantioselective Friedel-Crafts alkylations<sup>93</sup> and asymmetric transfer hydrogenations,<sup>93</sup> as well as asymmetric aldol condensations of ketones with isatins.<sup>94</sup>



**SCHEME 33.** Asymmetric Friedel-Crafts alkylations, organocatalytic transfer hydrogenations, and aldol condensations

In most cases, however, moderate yields and/or enantioselectivities have been obtained for these reactions (Scheme 33).

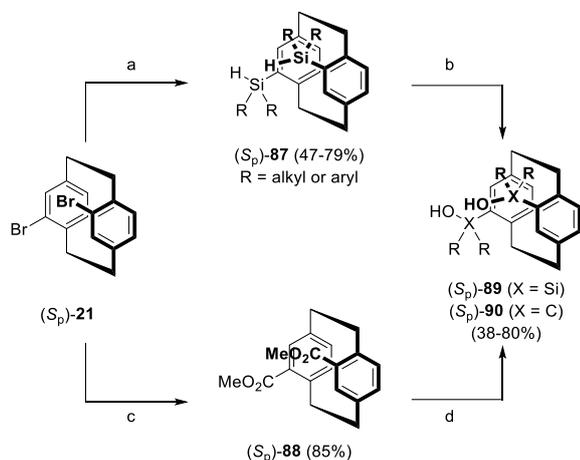
The pCp-based *pseudo-ortho* bis-thiourea derivative ( $R_p$ )-**78**, on the contrary, has proven to be a powerful and effective catalyst for enantioselective Henry reactions.<sup>95</sup> In the presence of this compound, several arylaldehydes have indeed been converted to the corresponding nitroalcohols in good yields and high enantiomeric excesses (up to 97% ee, Scheme 34).



**SCHEME 34.** Examples of asymmetric Henry reactions

### Diols and silanols

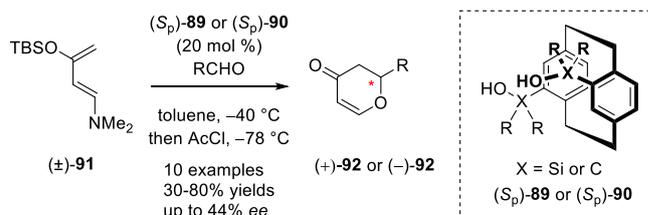
Aside from functionalized thiourea derivatives, different planar chiral H-bonding organocatalysts, which incorporate diol or bis-silanol moieties, have been developed taking advantage of the rigid conformation of the [2.2]paracyclophane scaffold.<sup>96</sup> These compounds have been prepared starting from enantiopure 4,12-dibromo-[2.2]-paracyclophane through a double metal-halogen exchange, followed by a reaction with either monochlorosilanes or methyl carbonate (Scheme 35). Different oxidation conditions have then been employed to convert the silylated intermediates ( $S_p$ )-**87** to the corresponding bis-silanols ( $S_p$ )-**89**. At the same time, the reduction of ester derivative ( $S_p$ )-**88** with various Grignard reagents has been carried out to access the desired diol products ( $S_p$ )-**90** (Scheme 35).



Reagents and conditions: a)  $t\text{-BuLi}$ , THF,  $-78^\circ\text{C}$ , then  $\text{R}_2\text{SiHCl}$ ; b)  $\text{KMnO}_4$ , or  $m\text{-CPBA}$ , or  $[\text{Ir}(1,5\text{-cod})\text{Cl}]_2$ , air/ $\text{H}_2\text{O}$ ; c)  $t\text{-BuLi}$ , THF,  $-78^\circ\text{C}$ , then  $(\text{MeO})_2\text{CO}$ ; d)  $\text{RMgBr}$ , THF

**SCHEME 35.** Synthesis of planar-chiral bis-silanols and diols

The catalytic activity of bis-silanols and diols has been tested in the hetero-Diels–Alder reaction of Rawal's diene with aliphatic or aromatic aldehydes.<sup>96</sup> Both types of catalysts can promote the asymmetric transformation, even if, in most cases, moderate enantioselectivities have been observed (44% ee at most, Scheme 36).

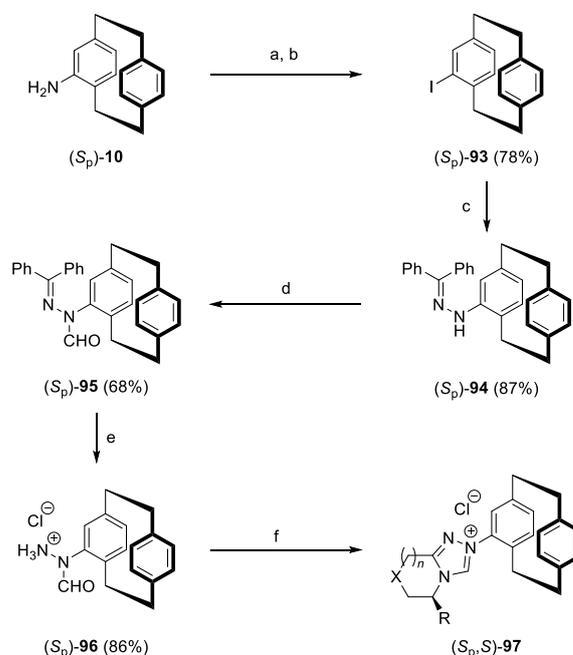


**SCHEME 36.** Hetero-Diels–Alder reactions promoted by pCp-based bis-silanols and diols

Enantiopure 4,12-dihydroxy[2.2]paracyclophane and its derivatives have been employed to promote asymmetric Diels–Alder reactions,<sup>97,98</sup> as well as the organocatalytic ring-opening of epoxides.<sup>98</sup> However, in these cases, racemic products or low enantiomeric excesses (<5% ee) have been obtained.

### N-Heterocyclic Carbenes (NHCs)

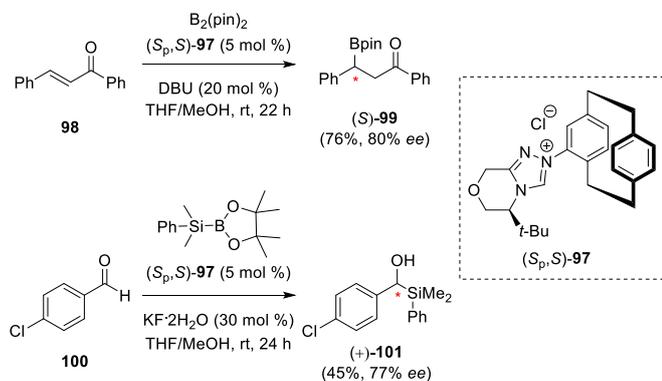
Planar chiral bicyclic 1,2,4-triazolium salts derived from [2.2]paracyclophane have been prepared and successfully applied in asymmetric organocatalysis.<sup>99-101</sup> The synthesis of these compounds starts from enantiopure 4-amino[2.2]paracyclophane (Scheme 37). The aniline derivative ( $S_p$ )-**10** is first converted to 4-iodo[2.2]paracyclophane ( $S_p$ )-**93** through the formation of a diazonium salt, and subsequent reaction with KI. A palladium-catalysed cross-coupling reaction then allows the preparation of the pCp-based benzophenone hydrazine ( $S_p$ )-**94** which can react with acetic anhydride and formic acid to generate the formylated product ( $S_p$ )-**95** in 68% yield (Scheme 37). Acid hydrolysis of this compound affords a formyl-protected hydrazine hydrochloride salt that can undergo a reaction with various imidate derivatives to generate different 1,2,4-triazolium salts ( $S_p,S$ )-**97** in high overall yields (Scheme 37).



Reagents and conditions: a)  $\text{HBF}_4$ , EtOH,  $60^\circ\text{C}$  10 min, then isoamyl nitrite,  $0^\circ\text{C}$ , 10 min; b)  $\text{KI}$ ,  $\text{I}_2$ , MeCN, rt, 3 h; c) Pd-DPPF, benzophenone hydrazone,  $\text{NaOtBu}$ , toluene,  $110^\circ\text{C}$ , 2 h; d)  $\text{Ac}_2\text{O}$ ,  $\text{HCOOH}$ ,  $50^\circ\text{C}$ , 36 h; e)  $\text{HCl}$  (4 M in EtOH),  $\text{H}_2\text{O}$ , rt, 3 h; f) imidate derivative, MeOH,  $50^\circ\text{C}$  2 h, then trimethyl orthoformate,  $\text{HCl}$  (4 M in EtOH),  $120^\circ\text{C}$ , 3 h.

**SCHEME 37.** Synthesis of 1,2,4-triazolium salts derived from [2.2]paracyclophane

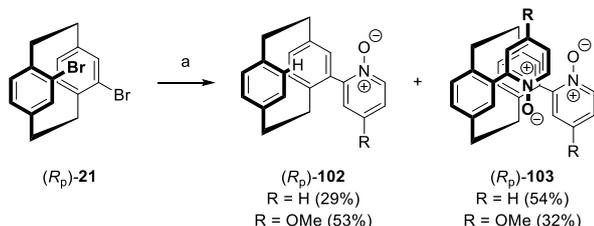
While products ( $S_p,S$ )-**97** have frequently been used as planar chiral NHC precursors in asymmetric transition metal catalysis,<sup>17,21</sup> only few examples of organocatalyzed transformations promoted by such compounds have been reported to date. These include the enantioselective  $\beta$ -boration of acyclic enones **98**<sup>99,100</sup> as well as the asymmetric 1,2-silylation of aromatic aldehydes **100** (Scheme 38).<sup>101</sup> Both reactions proceed smoothly in the presence of strong bases to afford the expected products in moderate to good yields and up to 77-80% ees.



**SCHEME 38.** Examples of asymmetric organocatalyzed transformations promoted by pCp-based NHC precursors

### Pyridine N-Oxides

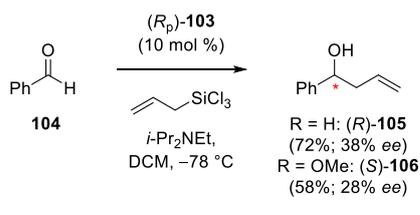
Although pyridine *N*-oxides have more often been employed as ligands for metal-based catalysis<sup>102</sup> or precursors for the development of photoelectronic dyes<sup>103</sup> and metal-organic frameworks,<sup>104</sup> these compounds have also revealed to be effective Lewis base organocatalysts in various transformations.<sup>105</sup> Planar chiral pyridine *N*-oxides derived from [2.2]paracyclophane have been synthesized through the direct arylation of enantiopure 4,12-dibromo[2.2]paracyclophane ( $R_p$ )-**21** (Scheme 39). This compound can indeed undergo a reaction with differently substituted pyridine *N*-oxides, in the presence of tri-*tert*-butylphosphonium tetrafluoroborate, palladium(II) acetate, and potassium carbonate, to afford mono- and di-substituted products ( $R_p$ )-**102** and ( $R_p$ )-**103** (Scheme 39).<sup>106</sup>



Reagents and conditions: a) *N*-oxide, Pd(OAc)<sub>2</sub>, *t*-Bu<sub>3</sub>P<sup>+</sup>BF<sub>4</sub><sup>-</sup>, K<sub>2</sub>CO<sub>3</sub>, toluene reflux

**SCHEME 39.** Synthesis of pCp-based pyridine *N*-oxide organocatalysts

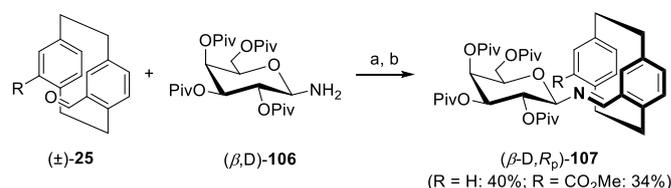
pCp-Based pyridine *N*-oxides ( $R_p$ )-**103** have been employed to promote the Lewis base-mediated allylation of benzaldehyde with allyltrichlorosilane (Scheme 40).<sup>106</sup> Even if the organocatalysts display a good activity, only modest enantioselectivities have been observed after the reactions (~28-38% ees). Interestingly, electronic factors appear to play a crucial role in these transformations: unsubstituted and electron-rich pyridine *N*-oxides furnish products with opposite absolute configuration, and comparable enantiomeric excess (Scheme 40).



**SCHEME 40.** Examples of Lewis base-mediated asymmetric reactions promoted by pCp-based pyridine *N*-oxides

### Imines

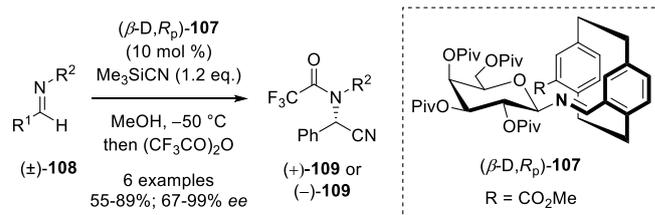
In 2007, planar chiral imine organocatalysts lacking hydrogen-bond-donor functions have been prepared through a condensation reaction between racemic aldehydes derived from [2.2]paracyclophane and 2,3,4,6-*tetra-O*-pivaloyl- $\beta$ -D-galactopyranosyl amine (Scheme 41).<sup>107</sup>



Reagents and conditions: a) Na<sub>2</sub>SO<sub>4</sub>, toluene; b) HPLC separation

**SCHEME 41.** Synthesis of *N*-galactosyl-[2.2]paracyclophane carbaldimines

After the separation of the two diastereomers by HPLC, the *pseudo-gem* di-substituted paracyclophanes featuring both imine and ester binding groups have been employed to promote enantioselective Strecker reactions leading to optically active  $\alpha$ -amino nitriles. High yields and enantioselectivities (up to 89%, and 99% ee) have been obtained in the presence of catalyst ( $\beta$ -D, $R_p$ )-**107** (Scheme 42).<sup>107</sup>

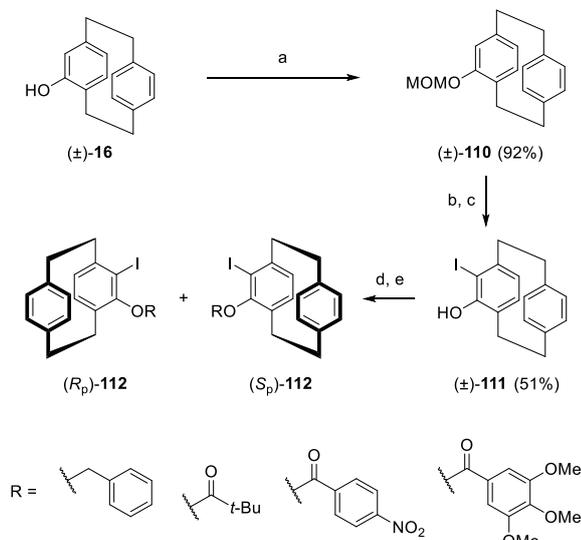


**SCHEME 42.** Enantioselective Strecker reactions promoted by pCp-based imine organocatalysts

### Iodoarenes

Recently, planar chiral iodoarenes derived from [2.2]paracyclophane have been successfully applied in hypervalent iodine catalysis.<sup>108</sup> The preparation of these derivatives, which are more frequently employed as key synthetic intermediates rather than as iodine-based organocatalysts, involves the derivatization of racemic 4-hydroxy[2.2]paracyclophane ( $\pm$ )-**16** (Scheme 43). After the protection of the free hydroxy group of this molecule as a MOM ether, metalation, followed by quenching with I<sub>2</sub> leads to the introduction of an iodine atom *ortho* to the oxygenated function. Removal of the protecting group under acidic conditions, and optical resolution by HPLC on a chiral stationary phase, afford

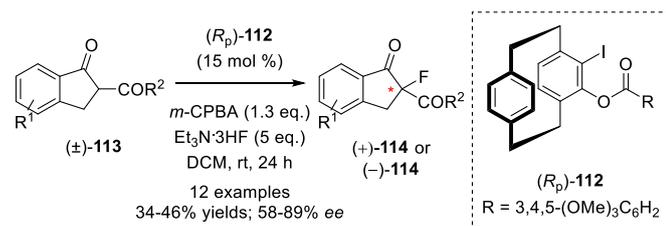
enantiopure intermediates ( $R_p$ )-**111** or ( $S_p$ )-**111** that can undergo alkylation or acylation reactions to generate differently functionalized products. Selected examples of these compounds (( $R_p$ )-**112** or ( $S_p$ )-**112**) are reported in Scheme 43.



Reagents and conditions: a) chloromethyl methyl ether, NaH, Et<sub>2</sub>O/DMF, 0 °C, 2 h; b) *n*-BuLi, TMEDA, Et<sub>2</sub>O, 0 °C, 1.5 h, then I<sub>2</sub>, 10 h rt; c) HCl<sub>aq</sub>, MeOH, reflux, 10 h; d) HPLC separation; e) BnBr or ROCl, K<sub>2</sub>CO<sub>3</sub>, acetone, 0 °C to rt, 10 h.

**SCHEME 43.** Synthesis of pCp-based iodoarenes.

The enantiopure pCp-based iodoarenes can be used to promote the asymmetric fluorination of  $\beta$ -ketoesters ( $\pm$ )-**113** with HF and *m*-CPBA. After a screening of paracyclophanes incorporating diverse functional groups, benzoylated derivatives have been identified as the best catalysts for this transformation (Scheme 44).<sup>108</sup> The nucleophilic fluorination tolerates cyclic  $\beta$ -ketoesters with both electron-donating and electron-withdrawing substituents. The reaction products have been isolated in up to 89% ee while using sterically hindered pCp catalysts. Acyclic compounds do not react, thus representing the limitation of this interesting approach.



**SCHEME 44.** Examples of nucleophilic fluorination reactions promoted by pCp-based iodoarenes

## Conclusion

In the first part of this review, we have described the different approaches that can be followed to access enantiopure [2.2]paracyclophanes. Although classical resolution methods relying on the preparation and separation of diastereoisomeric compounds or HPLC separations still dominate this research field, practical examples of kinetic resolutions and desymmetrization reactions have started to emerge in recent years. We expect these transformations, which constitute valuable alternatives to previously described time-consuming

and costly processes, to be increasingly employed as key synthetic procedures in paracyclophane chemistry in the near future.

Enantiopure [2.2]paracyclophanes have been extensively employed as building blocks for the development of planar chiral compounds with interesting physicochemical properties. In the second part of this review, we have outlined their use as catalysts in several metal-free asymmetric reactions. Considering their broad range of applications, we are firmly convinced that planar-chiral [2.2]paracyclophanes will continue to attract attention and grow in importance in the years to come.

## Acknowledgements

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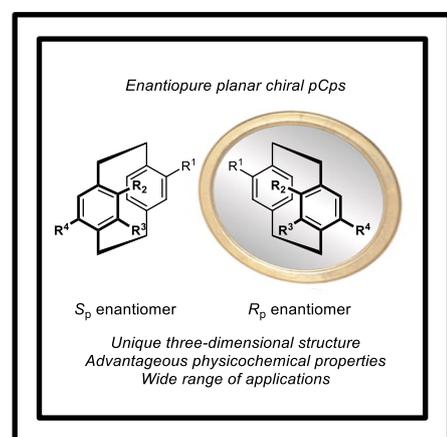
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## Graphical Abstract



Planar chiral [2.2]paracyclophanes (pCps) constitute a fascinating class of molecules which possesses an unusual three-dimensional core and intriguing physicochemical properties. This short review focuses on the synthesis of enantiopure pCps and their application in asymmetric organocatalysis.