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Asymmetric and fused heterocycles based on [2.2]paracyclophane

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1. Introduction

Heterocyclic compounds based on the [2.2]paracyclophane substructure have been known since the 1960s, but there has been an upsurge of interest in the past few years. The impetus for most studies is to create heterocycles having either planar chirality,[1] or the capacity for long-distance electronic communication; [2.2]paracyclophane offers both these possibilities. This review describes the synthesis and application of heterocycles based on [2.2]paracyclophane, organized into five structural types (Fig. 1): heterocycle pendant from benzene ring (type A), heterocycle fused to benzene ring (type B), heterocycle pendant from spanning bridge (type C), heterocycle fused to spanning bridge (type D), and heterocycle bridging the two benzene rings (type E). Within each structural type, the discussion is organized by heterocycle.

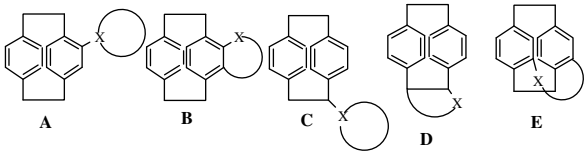
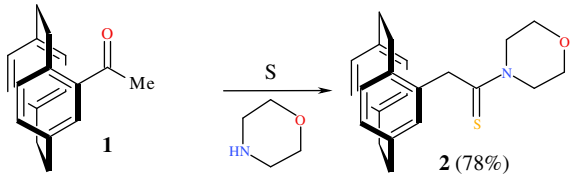


Figure 1. [2.2]Paracyclophane structural types.

2. Heterocycle pendant from benzene ring

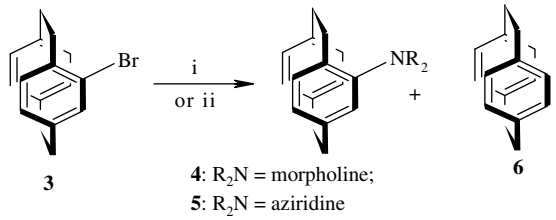
2.1. Morpholine

In 1967, Cram and Harris prepared the first heterocycle-bearing [2.2]paracyclophane as an intermediate in a Kindler–Willgerodt rearrangement. Reaction of 4-acetyl[2.2]paracyclophane (**1**) with elemental sulfur in boiling morpholine for 113 h afforded thioacetomorpholide **2** in 78% yield (Scheme 1).[2]



Scheme 1. Kindler–Willgerodt rearrangement of acetyl[2.2]paracyclophane.

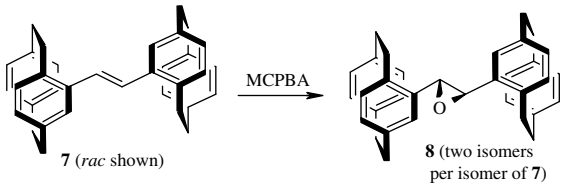
In two recent studies of conditions for Hartwig–Buchwald reactions, 4-bromo[2.2]-paracyclophane (**3**) has been coupled with morpholine[3] and aziridine[4] under slightly different conditions, to give **4** and **5**, respectively (Scheme 2). Non-heterocyclic primary amines coupled with **3** in good yields, and *N*-arylaziridines and *N*-arylmorpholines were obtained in good yields from bromides with only one aryl nucleus, but the highest yield of **4** was 38%, and that of **5** was 17%. The major reaction product in each case was [2.2]paracyclophane (**6**) itself, apparently because the bulky aryl partner favors β-hydride elimination (to give **6**) over reductive elimination to give **4** or **5**.[3,4]



Scheme 2. Morpholination or aziridination of 4-bromo[2.2]paracyclophane. (i) Morpholine (1.2 equiv), $Pd_2(dba)_3$ (2.5 mol %), Binap (5 mol %), *t*-BuONa (2 equiv), diglyme (1 equiv), toluene, 75 °C, 16 h (**4** 38%); (ii) aziridine (2 equiv) $Pd(OAc)_2$ (3 mol %), Xantphos (4 mol %), Cs_2CO_3 (2 equiv), toluene, 100 °C, 3 d (**5**, 17%).

2.2. Oxirane

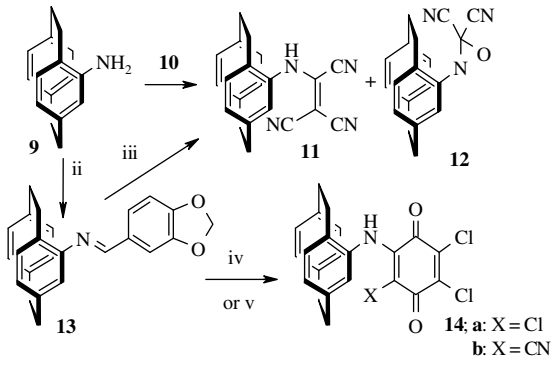
To differentiate the diastereomeric *trans*-1,2-bis([2.2]paracyclophanyl)ethenes *rac*- and *meso*-**7**, they were epoxidized with MCPBA (Scheme 3).[5] From *meso*-**7**, enantiomeric epoxides **8** were formed, which thus had identical arrival times in ion-mobility mass spectrometry; *rac*-**7** gave diastereomeric epoxides with different arrival times.



Scheme 3. Epoxidation of 1,2-bis(paracyclophanyl)ethenes. Yield not stated.

2.3. Oxaziridine, benzodioxole

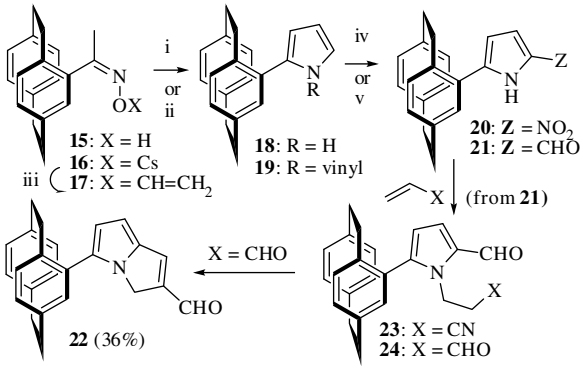
In 1993, the Mourad et al. reported that reaction of 4-amino[2.2]-paracyclophane (**9**) with 1,1,2,2-tetracyanoethylene (**10**, TCNE) furnished olefin **11** and oxaziridine **12** (Scheme 4).[6] The interpretation was that initial charge-transfer complexation between **9** and **10** led to a formal conjugate adduct, which reacted further in one of two directions. Loss of HCN gave **11**, while loss of malononitrile followed by addition of water and then cyclization provided **12**.[6] Later, it was reported that **9** and piperonal form the Schiff base **13**.[7] It was subsequently found that **13** reacts with an assortment of electron-deficient π-systems by charge transfer, followed by loss of piperonal and the conjugate acid of a leaving group, to give formal addition/elimination products such as **11** and **14ab**: Scheme 4 shows a non-exhaustive sampling. Oxaziridine formation, as observed from free **9** with TCNE, is not observed from **13**.[8]



Scheme 4. Reaction of 4-amino[2.2]paracyclophane and its imine with oxidants. (i) **10** (EtOAc, **11** 41%, **12** 31%); (ii) piperonal (yield not stated); (iii) TCNE, EtOAc (**11** 50%); (iv) *p*-chloranil, EtOAc (**14a** 29%), (v) DDQ, EtOAc (**14b** 25%).

2.4. Pyrrole, pyrrolizine, pyrroline, pyrrolone, imidazolidone, isoxazoline, benzisoxazoline, isoxazolidine, oxathiazolidine

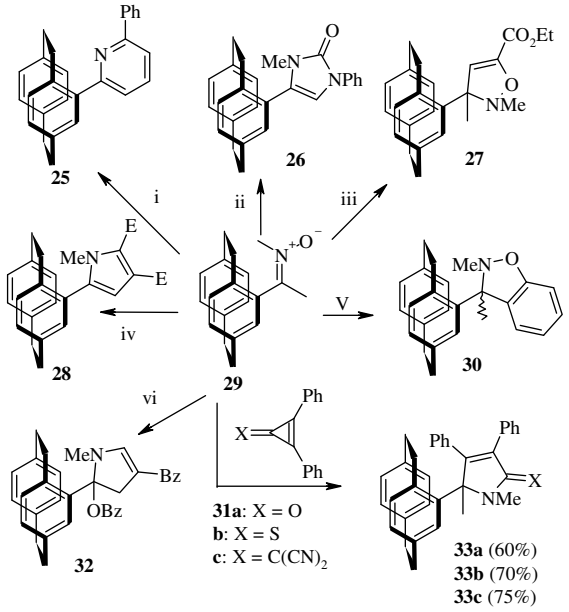
Two Russian groups have elaborated acetyl[2.2]paracyclophane oxime (**15**) to 4-(2′-pyrrolyl)[2.2]paracyclophane (**18**). Treatment of **15** with acetylene and KOH or RbOH in DMSO gave **18** in 9–22% yield, along with an assortment of side products including *N*-vinyl derivative **19**.[9] The pre-prepared Cs salt of **15** (i.e., **16**) reacted with acetylene in a biphasic DMSO-pentane system in an autoclave to give vinyl ether **17** in 78% yield. Thermolysis of **17** then furnished **18** in 53% isolated yield.[10] Once formed, **18** underwent electrophilic nitration to give **20**, and formylation to give **21**. In turn, **21** added in conjugate fashion to acrylonitrile to provide **23**, and to acrolein to furnish pyrrolizine **22**, the latter presumably via cyclization of adduct **24** (Scheme 5).[9] One of these



Scheme 5. Preparation and elaboration of 4-(2′-pyrrolyl)[2.2]paracyclophane: (i) (from **15**) acetylene, MOH, DMSO; [KOH: **18** (22%) and **17** (6%); RbOH: **18** (14%) and **19** (14%)]; (ii) (from **17**) DMSO, 120 °C, 30 min (**18** 53%); (iii) (from **16**) acetylene, DMSO/pentane, 70 °C (autoclave), 5 min (**17** 78%); (iv) (from **18**) $Cu(NO_3)_2$, Ac_2O (**20** 34%); (v) (from **18**) DMF, $POCl_3$ (**21** 69%).

groups expressed the intention to elaborate **18** to BODIPY derivatives;[10] that report (which would be most interesting!) has not yet appeared.

Aly et al. reported that nitrone **29**, prepared from 4-acetyl[2.2]-paracyclophane (**1**, its structure was proved by X-ray structure analysis to have the *E*-form) and *N*-methylhydroxylamine,[11] has been elaborated to a variety of heterocyclic products. Depending on the partner, **29** reacts either as a nitrone, or via its enamine tautomer; in turn, the enamine can react to form either five- or six-membered heterocycles. Reaction of **29** with dibenzoylethylene furnished the pyridine **25**.[7] This result was attributed to the enamine adding to dibenzoylethylene in conjugate fashion, followed by cyclization, extrusion of benzoic acid, and aromatization to give **25**. The reactions of **29** with phenyl isocyanate and dimethyl acetylenedicarboxylate (DMAD) also proceed via the enamine, but in [3+2] fashion to provide imidazolone **26** and pyrrole **28**, respectively. With ethyl propiolate and benzyne, **29** enters into classic nitrone [3+2] cycloadditions to give isoxazoline **27** and the stereoisomeric benzoisoxazolines **30** respectively.[12] One of the isolated diasteromers of compounds **30** was structurally proved by X-ray structural analysis. The structure of that isomer indicates that the heterocyclic ring, selected dimensions of which are given in the caption, adopts an envelope conformation in which the nitrogen atom lies 0.45 Å out of the plane of the other four atoms (mean deviation 0.002 Å). Other dimensions may be regarded as normal. Recently, Aly reported that reactions of **29** with diphenylcyclopropenones **31a–c** and dibenzoylacetylene have been found to furnish pyrrolone derivatives **33a–c** and pyrroline **32**, respectively (Scheme 6).[13]

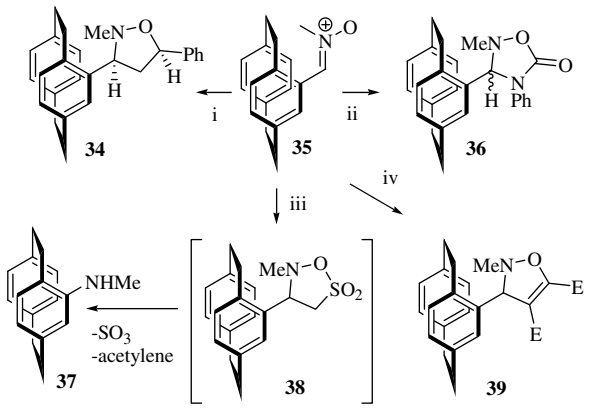


Scheme 6. (**E**=**CO$_2$Me** and **Bz**=**PhCO**). Cycloadditions of nitrone **29**. (i) BzCH=CHBz, PhMe, reflux (70%); (ii) PhN=C=O, PhMe, reflux (60%); (iii) HC≡CCO_2Et, PhMe, reflux (67%); (iv) DMAD, PhMe, reflux (60%); (v) benzenediazonium carboxylate, MeCN, reflux (62% as 1:1 mixture); (vi) BzC≡CBz, PhMe, reflux (70%).

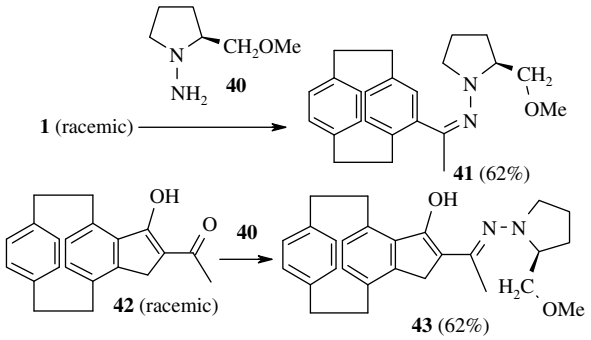
Aly also reported that the related nitrone **35** (its structure was proved by X-ray structure analysis to have the *Z*-diastereomer) cannot tautomerize to an enamine and thus reacts only as a [3+2] dipole. With styrene, **35** provides the isoxazolidine **34**; with phenyl isocyanate, the 1,2,4-oxadiazol-5-one **36**; and with DMAD, the isoxazoline **39**. When methylene sulfene is generated in the presence of **35**, the product is methyl [2.2]paracyclophan-4-yl amine (**37**), attributed to fragmentation of the 1,2,5-oxathiazolidine *S*,*S*-dioxide **38** (Scheme 7).[14]

2.5. Pyrrolidine

Compound **1**[15] and the β-diketone **42**[16] have been resolved via their SAMP-hydrazone derivatives. Reaction of **1** and **42** with SAMP



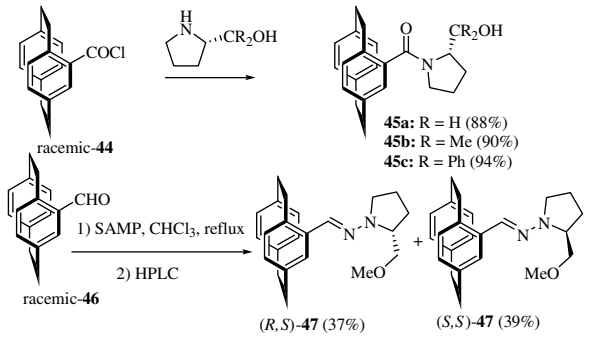
Scheme 7. (**E**=**CO$_2$Me**). Cycloadditions of nitrone **35**. (i) Styrene, PhH, reflux (68%); (ii) PhN=C=O, PhH, reflux (90%, 1:1); (iii) [CH_2=SO_2] from MsCl and Et_3N, PhH, 60 °C (**37** 80%); (iv) DMAD, PhH, reflux (61%).



Scheme 8. Resolution via SAMP-hydrazones.

(**40**) respectively gave **41** and **43** as separable diastereomers (Scheme 8). After separation, hydrolysis with oxalic acid furnished enantiomerically pure **1** and **42**; SAMP was recovered.[15,16]

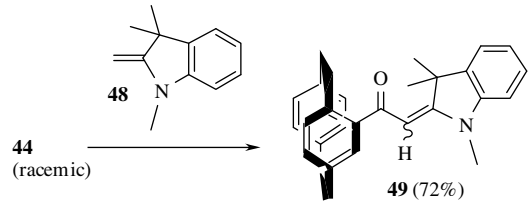
A Japanese group has treated racemic [2.2]paracyclophane-4-carbonyl chloride (**44**) with (*S*)-prolinol derivatives to give tertiary amides **45a–c**, each as a pair of optically active diastereomers after separation (Scheme 9).[17a] Enders[17b] has recently reported that enantiomeric *N*-pyrrole derivatives were obtained on condensation of the racemic paracyclophanyl-aldehyde **46** with SAMP in chloroform. The resulting racemic pyrroles were separated by HPLC as (*R*,*S*)-**47** and (*S*,*S*)-**47** as shown in Scheme 9.



Scheme 9. Prolinol amides of [2.2]paracyclophane-4-carboxylic acids **45**. Enantiomeric preparation and separation of (*R*,*S*)- and (*S*,*S*)-*N*-pyrroles **47**.

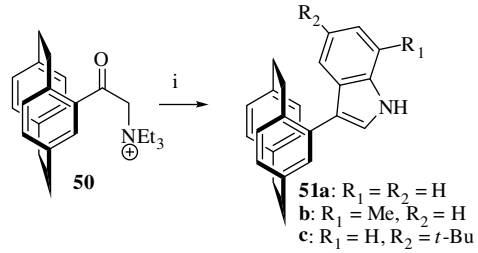
2.6. Indole and benzo-fused indoles

In 1990, seeking to resolve [2.2]paracyclophane-4-carboxylic acid, Hopf reacted acid chloride **44** with the 'Fischer base' **48** to provide vinylogous amide **49** as a mixture of both *E*/*Z* and planar-chiral isomers (Scheme 10). The planar-chiral isomers of **49** could be separated by HPLC.[18]



Scheme 10. Reaction of [2.2]paracyclophane-4-carbonyl chloride with the Fischer base.

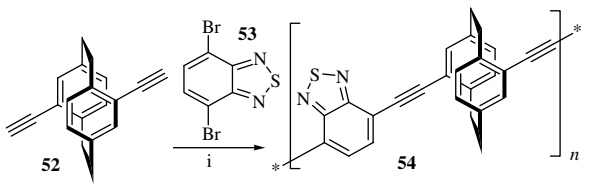
It has been found that the reaction of 4-[α-(triethyl-ammonio)acetyl]-[2.2]paracyclophane (**50**) with anilines or α-naphthylamine furnished the corresponding indoles (**51a–c**) via the Bischler reaction (Scheme 11).[19]



Scheme 11. Bischler syntheses of 4-(2′-indolyl)[2.2]paracyclophanes. (i) 2-(R_1)-4-(R_2)-aniline, 185–200 °C (**51a** 46%, **51b** 43%, **51c** 47%); (ii) α-naphthylamine, 200 °C (46%).

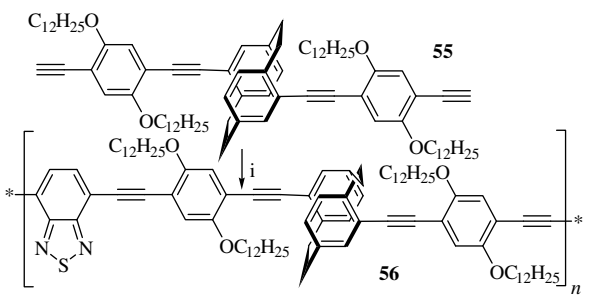
2.7. Benzothiadiazole, carbazole, xanthene

Chujo has prepared numerous through-space conjugated polymers based on cyclophanes.[20] They are structural variants of poly-(phenyleneethynylene), subunits being chosen to tune the polymers' spectroscopic and electrochemical properties for application to polymer-based photonic and electronic devices. In 2004, this group entered the realm of heterocyclic chemistry by polymerizing 4,11-diethynyl[2.2]paracyclophane (**52**) with 4,7-dibromo-2,1,3-benzothiadiazole (**53**) under Sonogashira conditions to provide **54** (Scheme 12). This polymer has a weight-average molecular weight (M_w) of 1400 and a molecular-weight distribution (M_w/M_n) of 1.4, giving a number-average degree of polymerization for **54** of about three. The relatively low molecular weight was attributed to low solubility.[21]



Scheme 12. Synthesis of paracyclophane-benzothiadiazole polymer. (i) $PdCl_2PPh_2$, PPh_3, CuI, THF/Et_3N, 50 °C, 48 h (66%).

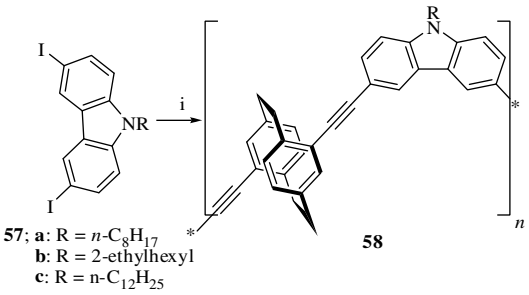
For higher solubility, **55** was polymerized with monomer **53** to afford polymer **56** (Scheme 13). This polymer had $M_w \approx 83{,}000$ and



Scheme 13. Synthesis of solubilized cyclophane-benzothiadiazole polymer. (i) **53**, $PdCl_2PPh_2$, PPh_3, CuI, THF/Et_3N (96%).

M_w/M_n=2.6, yielding an estimated *n* of 23. It was found to be thermally stable and soluble in organic solvents, and gave transparent uniform thin films by casting or spin-coating. Its absorption maximum was 470 nm, compared to that (ca. 460 nm) of the model compound containing the dialkoxybenzene and dialkynylbenzothiadiazole subunits, but lacking the cyclophane; this indicates through-space conjugation through the paracyclophane subunit of **56**. Polymer **56** exhibited orange fluorescence in solution and as a spin-coated film (λ_{max}=565 nm); annealing of the film created a second emission at 660 nm from intermolecular excimer formation.[21]

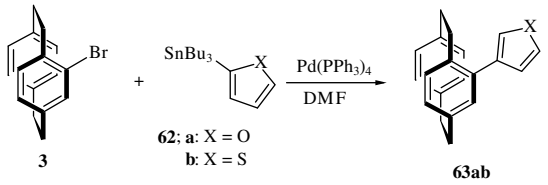
The same group polymerized **52** with 3,6-diiodo-*N*-alkylcarbazoles **57a–c** to provide **58a–c** (Scheme 14). These polymers have M_w=6800–10,100 and M_w/M_n of 1.8–2.5, giving an estimated *n* for **58a** of eight; they are thermally stable and soluble in organic solvents, and gave transparent uniform thin films by casting or spin-coating. They exhibit strong blue photoluminescence in solution and bluish-green photoluminescence in the solid state.[22]



Scheme 14. Synthesis of paracyclophane-carbazole polymers. (i) **52**, $PdCl_2PPh_2$, PPh_3, CuI, THF/Et_3N, reflux, 72 h (**58a** 54%, **58b** 30% **58c** 78%).

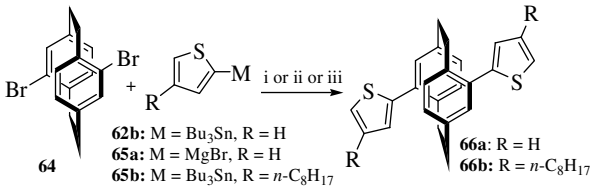
Polymerization of **52** with diiodoxanthene **59** and ethynylferrocene (**60**) in varying proportions gave 89–96% yields of **61**, which comprise alternating xanthene and cyclophane subunits (one more xanthene than cyclophane) between ferrocene end groups (Scheme 15). The mole ratio of **52**/**59**/**60** ranged from 2:3:2 to 9:10:2, which gave number-average molecular weights (M_n) of 2750–9000 and degrees of polymerization from three or four, to 15. The polymers gave almost identical UV–vis absorption spectra and fluorescence emission spectra, and cyclic voltammetry showed simultaneous (i.e., independent) oxidation of the terminal ferrocenes; thus, effective π–π stacking between cyclophane units is not achieved in solution.[23]

somewhat boat-shaped. The heterocyclic side chains were twisted versus the four coplanar carbons of the attached benzene ring, by 25 °C in **63a** and by 33–35 °C in **63b**.

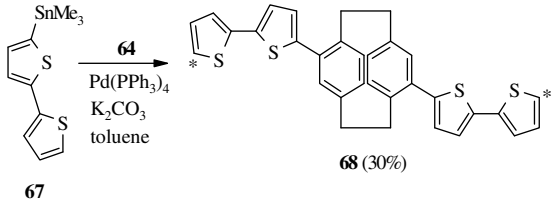


Scheme 16. Synthesis of 4-(2′-furyl)- and -thienyl)[2.2]paracyclophanes (**63a** 66%, **63b** 58%).

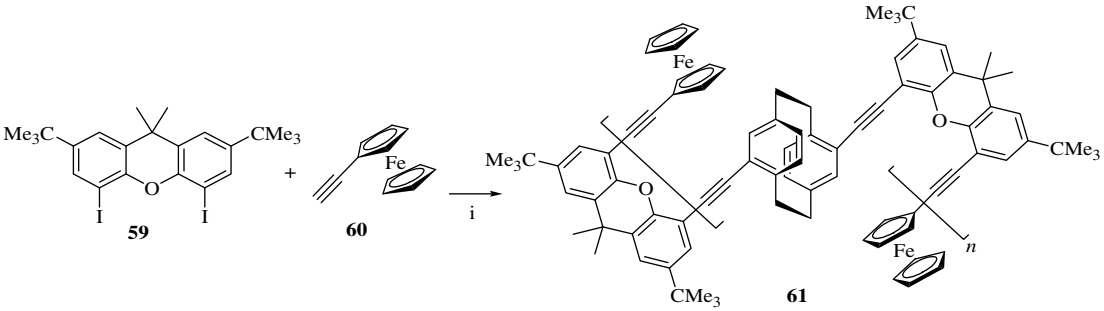
Extensive development of related structures began in short order. Collard has reported that **66a** can be prepared either by Ni^{II}-catalyzed coupling of 4,12-dibromo[2.2]paracyclophane (**64**) with (2-thienyl)-magnesium bromide (**65a**),[25] or by Stille coupling of **64** with **62b** (Scheme 17).[26] The soluble analogue **66b** was prepared similarly, from **64** and **65b.** Cyclic voltammetry (CV) indicated that **66a** has an oxidation potential ca. 0.7 mV lower than the unstacked models, (2-thienyl)benzene or 1,4-bis(2′-thienyl)-benzene.[25]



Scheme 17. Preparation of 4,11-bis(2′-thienyl)[2.2]paracyclophane. (i) **65a**, Ni(dppp)Cl_2, THF (**66a**, yield not stated); (ii) **62b**, Stille conditions (**66a**, yield not stated); (iii) **65b**, $Pd(PPh_3)_4$ (**66b**, yield not stated).



Scheme 18. Synthesis of 4,11-bis(dithienyl)[2.2]paracyclophane (**68**).



Scheme 15. Xanthene-cyclophane polymers with ferrocene end groups. (i) **52**, $PdCl_2(PPH_3)_2$, PPh_3, CuI, THF–Et_3N, 50 °C, 48 h (89–96%).

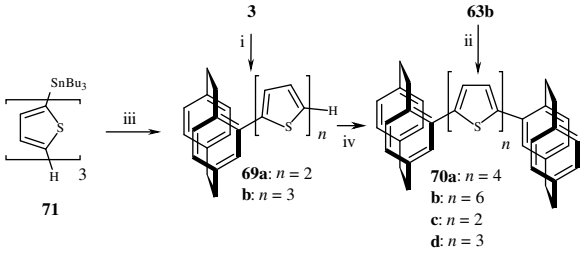
2.8. Furan, thiophene

The parent 4-(2′-furyl)- and -(2′-thienyl)-[2.2]paracyclophanes (**63a**,**b**) were prepared in 1999 by Hopf, who coupled **3** with tributyl-(2-furyl)- and -(2-thienyl)-stannanes (**62a**,**b**) under Pd(0) catalysis (Scheme 16).[24] In crystal structures, the [2.2]paracyclophane subunits were very similar to those of [2.2]-paracyclophane itself and to the subunit in other structures, the benzene rings being

Stille-type coupling of **64** with the (dithienyl)stannane **67** gave **68**, which could be polymerized electrochemically (Scheme 18).[27] Polymerization takes place by coupling the starred positions of monomer **68**, i.e., the polymer intersperses quaterthienyl and [2.2]paracyclophane subunits.

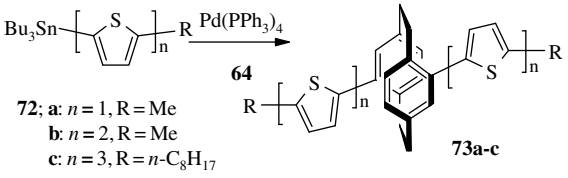
Stille coupling of **3** with **67** gave mono-(dithienyl)paracyclophane **69a**, which could be oxidized with $FeCl_3$ to give **70a**.[27b,28] Similarly, Stille coupling of **3** with **71** gave **69b**, which could be

oxidized to **70b** (Scheme 19). Although **63b** is a lower 'thienologue' of **70a** and **70b**, reaction of **63b** with $FeCl_3$ did *not* give **70c**; this result was attributed to the high oxidation potential of **63b**.[28] Coupling of **63b** to give **70c** required lithiation followed by coupling with cupric chloride.[29] The coupling of **3** with **71** also produced a small amount of **70d**, which was ascribed to deprotonation of **69b** under the Stille conditions, followed by coupling with a second molecule of **3**.[28] The cation radical electrogenerated from **69a** is highly unstable, apparently due to coupling. By contrast, electro-oxidation of **70a–d** results in successive formation of the cation radicals and dications in all cases, all stable on the CV time scale. This behavior suggests that some charge must be stabilized on the cyclophane rings.[28]



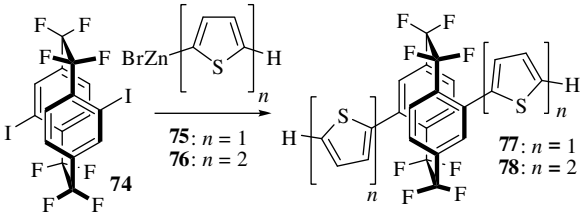
Scheme 19. Syntheses of bis([2.2]paracyclophanyl)oligo-thiophenes. (i) **67**, $Pd(PPh_3)_4$, PhMe (**69a** 60%); (ii) (1) BuLi, (2) $CuCl_2$ (**70c** yield n.s.); (iii) **3**, $Pd(PPh_3)_4$, PhMe (**69b** 70%, **70d** 10%); (iv) $FeCl_3$, CH_2Cl_2, rt (**70a** from **69a**, **75b** from **69b** yields not stated).

In 2002, Collard found that Stille coupling of **64** with stannanes **72a–c** provided thienylcyclophanes **73a–c** (Scheme 20).[29] Blocked from polymerizing by the substituents on the end thiophene rings, compound **73b** undergoes oxidation to form stable radical cations and dications, and its π-stacking changes the oxidation potentials of identical subunits.[29,30]



Scheme 20. Oxidatively blocked bis(oligothienyl)[2.2]paracyclophanes (70–80% crude, <40% isol.).

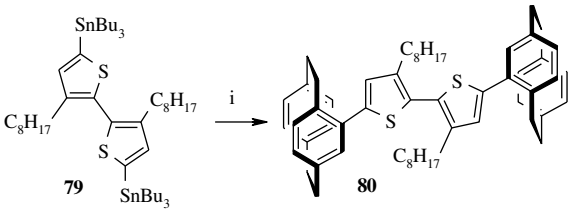
Bridge-fluorinated analogues of **66** and **68** were prepared by Negishi coupling of fluorinated cyclophane **74** with the thienylzinc reagents **75** and **76** (Scheme 21).[31] Electro-oxidation of the products **77** and **78** again led to polymerization. Poly(**77**) was of poor quality, but poly(**78**) gave well-defined cyclic voltammograms similar to those of polythiophene.



Scheme 21. Syntheses of bridge-fluorinated bis(oligothienyl)[2.2]paracyclophanes. (i) $Pd(PPh_3)_4$, THF, 50–60 °C (**77** yield not stated, **78** 87%).

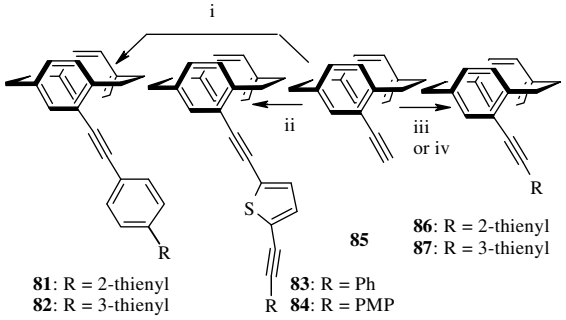
In 2003, Salhi and Collard prepared **80**, a soluble analogue of **70c**, by Stille coupling of **3** with **79** (Scheme 22). Compound **80** did *not* show stacking effects in its voltammograms.[26]

In 2006, the Perugia group reported the synthesis of thienyl cyclophanes **81–84**, **86**, and **87**, by Sonogashira coupling of 4-ethynyl[2.2]paracyclophane (**85**) with the corresponding iodides (Scheme 23). Each of these products consists of alternating aryl and



Scheme 22. An organic-soluble 5,5′-bis(paracyclophanyl)-2,2′-dithienyl. (i) **3**, $Pd(PPh_3)_4$, DMF.

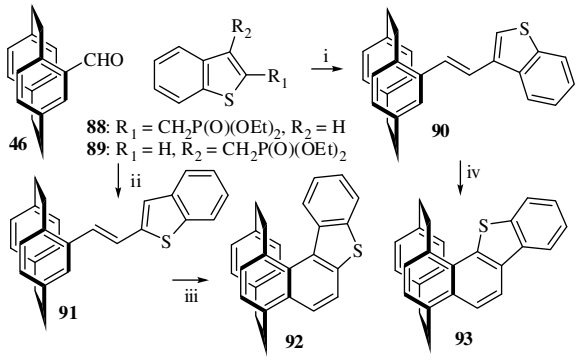
ethynyl substructures. The UV absorption maxima are at longer wavelengths (λ_{max}=330–362 nm) for the more extended **81–84** than for the less extended **86** and **87** (λ_{max}=299–319 nm); **83** and **84** show bathochromic shifts versus **81** and **82**, the thienyl rings of which are farther from the paracyclophane system.[32,33]



Scheme 23. Synthesis of [2.2]paracyclophanes with thienyl groups on spacers. (i) 1-iodo-4-[(2- or 3-thienyl)ethynyl]benzene, $PdCl_2(PPh_3)_2$, CuI, THF, rt (**81** 79%, **82** 82%); (ii) 2-iodo-5-(*R*-ethynyl)thiophene, $PdCl_2(PPh_3)_2$, CuI, THF, rt (**83** 48%, **84** 63%); (iii) 2-bromothiophene, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, 50 °C (**86** 85%); (iv) 2- or 3-iodothiophene, $PdCl_2(PPh_3)_2$, CuI, THF, 75 °C (**86** 99%, **87** 97%).

2.9. Benzo[*b*]thiophene

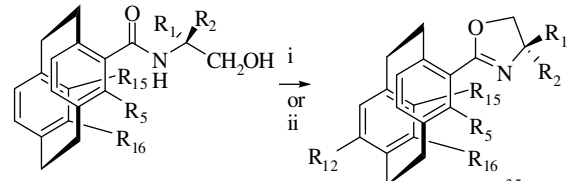
In 2007, Hopf reported that olefination by the regioisomeric phosphonates **88** and **89** of paracyclophane-carboxaldehyde **46** gave olefins **90** and **91**, respectively. In turn, photocyclization of **90** furnished thiahelicenophane **93**, and **91** gave **92** (Scheme 24).[34] Other thiahelicenophanes are discussed below (Section 3.9).



Scheme 24. Synthesis of thiahelicenophanes from [2.2]paracyclophane-4-carbaldehyde. (i) (**90** from **89**); (ii) (**91** from **88**) (iii) *hν*, I_2, biacetyl, PhMe (56%); (iv) *hν*, I_2, biacetyl, PhMe (42%).

2.10. Oxazoline

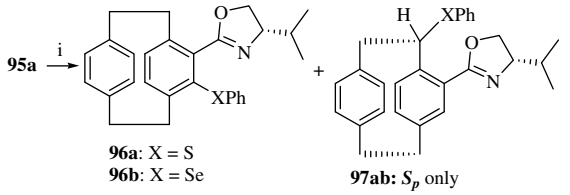
Numerous oxazoline-bearing [2.2]paracyclophanes (**95a–m**) have been prepared by cyclizing the corresponding *N*-(β-hydroxyethyl)-carboxamides **94a–m** (Scheme 25). When the side chain contains a chiral center, the oxazolino paracyclophane has both planar and central chirality.[35–42]



94a: $R_1 = R_5 = R_{15} = R_{16} = H$, $R_2 = iPr$ — **95a** (96%)[35a]
b: $R_1 = R_5 = R_{16} = H$, $R_2 = iPr$, $R_{15} = Br$ — **b** (91-95%)[37]
c: $R_1 = R_5 = R_{16} = H$, $R_2 = tBu$, $R_{15} = Br$ — **c** (91-95%)[37]
d: $R_1 = R_5 = R_{16} = H$, $R_2 = Bn$, $R_{15} = Br$ — **d** (91-95%)[37]
e: $R_1 = Ph$, $R_2 = R_5 = R_{16} = H$, $R_{15} = Br$ — **e** (91-95%)[37]
f: $R_1 = R_5 = R_{15} = R_{16} = H$, $R_2 = tBu$ — **f** (83%)[38]
g: $R_1 = R_2 = Me$, $R_5 = R_{15} = R_{16} = H$ — **g** (95%)[39]
h: $R_1 = R_2 = Me$, $R_5 = R_{16} = H$, $R_{15} = Br$ — **h** (97%)[39]
i: $R_1 = R_2 = Me$, $R_5 = R_{15} = H$, $R_{16} = Br$ — **i** (99%)[42]
j: $R_1 = R_5 = R_{15} = H$, $R_2 = iPr$, $R_{16} = Br$ — **j** (80%)[40]
k: $R_1 = R_5 = R_{15} = H$, $R_2 = tBu$, $R_{16} = Br$ — **k** (81%)[42]
l: $R_1 = Ph$, $R_2 = R_5 = R_{15} = H$, $R_{16} = Br$ — **l** (80-97%)[40]
m: $R_1 = R_{15} = R_{16} = H$, $R_2 = iPr$, $R_5 = OH$ — **m** (94-96%)[41]
95n ($R_5 = OTf$) (73%)[40]

Scheme 25. Oxazolino-paracyclophanes. (i) Tf_2O, pyridine (**94m** to **95n**); (ii) PPh_3, CCl_4, Et_3N, MeCN (all other closures).

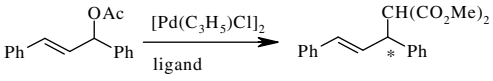
Oxazoline-templated lithiation of **95a** followed by electrophilic sulfenylation or selenenylation gave in each case an *ortho*-substituted product, again as a mixture at the chiral plane (S_p- and R_p-**96ab**; Scheme 26). In addition, each substitution gave an isomer substituted at the benzylic carbon nearest the oxazoline ring, from the side proximal to the oxazoline (**97ab**). Curiously, **97ab** are *not* formed as planar-chiral mixtures: the electrophiles seem to approach only from the concave face of the isopropyloxazoline ring, giving (S_p) chirality.[35]



96a: X = S
96b: X = Se
97ab: S_p only

Scheme 26. Oxazolinyl thio- and seleno-ethers. (i) (1) BuLi/TMEDA, (2) PhXXPh (X=S, Se). X=S: (S_p)-**96a** 28%, (R_p)-**96a** 19%, (S_p)-**97a** 12%. X=Se: (S_p)-**95b** 31%, (R_p)-**96b** 18%, (S_p)-**97b** 15%.

The six ligands (S_p)-**96ab**, (R_p)-**96ab**, and (S_p)-**97ab** were assessed individually in Pd-catalyzed allylic substitution (Eq. 1); **97ab**, bearing substituents in the benzylic position, were the most active and gave the highest asymmetric induction (93–94% ee). The asymmetric inductions of **97a** and **97b** were essentially indistinguishable; **97a** was slightly more active, giving 98% yield in 1.5 h under the test conditions, vs 2 h with **97b**. With the ring-substituted ligands, the sense of asymmetric induction depended on the sense of planar chirality: (S_p)-**96ab** led to (*R*) product, while (R_p)-**96ab** led to (*S*) product. By contrast, ligands **97ab** are (S_p), but gave (*S*) product.[35,36]

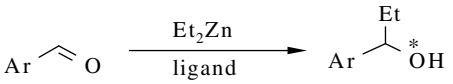


(1)

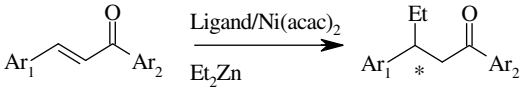
Many substituted oxazolinoparacyclophanes are available by bromine–lithium exchange followed by electrophilic capture. For example, lithiation of pseudo-geminal bromo oxazolino paracyclophanes **95b–e** and capture by benzophenone furnished **98b–e**;[37] other carbonyl electrophiles gave ligands **99b–e** and **100b–f**, all as mixtures around their chiral planes (Scheme 27).[43] Similarly, lithiation of **95b–e** followed by capture with chloro-diphenylphosphine gave oxazolinyl phosphines **101b–e**; to modulate the electron density at phosphorus, the organolithium derived from **95e** was captured with phosphines of varying electron density, to give compounds **101e–105e**.[44] The organolithium from **95h** could be phosphinylated to phosphine **100h**, sulfenylated to sulfide **106h**, or carboxylated to acid **107h**.[39] Starting with **95b** or **95c**, lithiation, trapping with trimethyl borate, and oxidation furnished hydroxy oxazolines **108bc**.[41]

In the pseudo-*ortho* series, lithiation of **95jl** followed by trapping with chlorophosphines led to **109j** and **110jl**. Planar-chiral diastereomers of the products could be separated (Scheme 28).[40] Lithiation of **95j** was followed by trapping with trimethyl borate and oxidation to furnish the hydroxy oxazolines **111j**, which were inseparable as such, but could be separated as their benzyl ethers **112j**. Cleavage of the separated ethers gave the individual hydroxy oxazolines **111j**.[41]

As ligands for the asymmetric addition of diethylzinc to aromatic aldehydes (Eq. 2), **98b–e** showed large ranges of both activity and asymmetric induction, the latter in both amount and sense. In additions to benzaldehyde, the configuration of the new chiral center matched the planar configuration around the oxazoline-bearing benzene ring of the paracyclophane, and greatest activity was observed when this chirality was opposite to the sense of the chiral center on the oxazoline ring, in **98b** or **98d**. This isomer of ligand **98d** was equally effective for additions to several other arene-carbaldehydes.[37] The optimum degree of flexibility is an old question in catalysis, the answer varying from system to system; ligands **99** and **100** were designed to be somewhat more flexible than **98**. In additions of diethylzinc to various arenecarbaldehydes (Eq. 2), the same match/mismatch effects of chirality on activity and asymmetric induction were observed as in **98**, and the best ligand of all three series was the isomer of **99d** with the same stereochemistry as the best isomer of **98d**.[43] Ligands **98–100** were also studied in the Ni-catalyzed asymmetric addition of diethylzinc to chalcones (Eq. 3). Chalcone is more sterically demanding than benzaldehyde, and in this system best enantioselectivity was obtained using **100c**, which is more flexible than ligands of series **99**.[45]



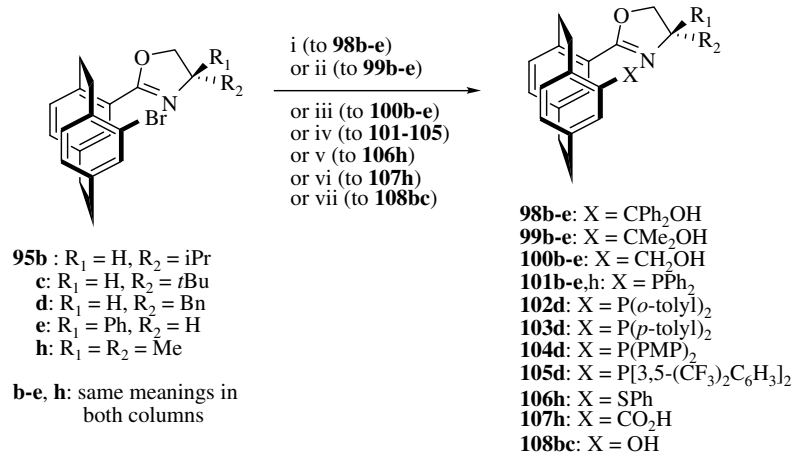
(2)



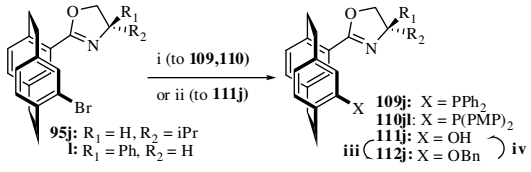
(3)

In palladium-catalyzed allylic alkylation (Eq. 1), ligands **105** led to high activity but the ee was 62% at best: as noted above, **101ab** gave 93–94% ee in this reaction. Allylic alkylations using **102d–105d** gave widely varying enantioselectivity, the fastest and most selective reaction being obtained with **104d** (98% yield in 20 min at 25 °C, 90% ee).[44,46]

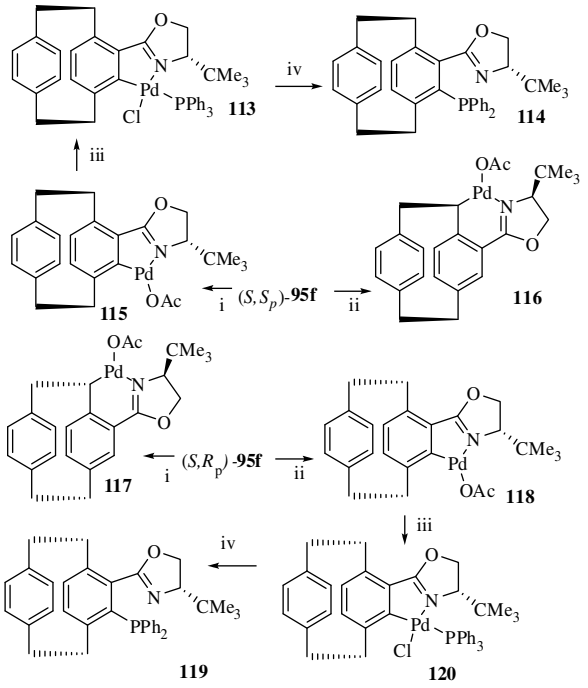
Palladation of oxazolino paracyclophane **95f** was regioselective in a sense that depended on solvent. In acetic acid, reaction of (S,R_p)-**95f** with palladium acetate took place *ortho* to the oxazoline, to furnish complex **118**; by contrast, palladation of (S,S_p)-**95f** took place at the proximal benzylic position to give **116**. In toluene as solvent, however, (S,R_p)-**95f** underwent benzylic palladation to give **117**, and (S,S_p)-**95f** suffered *ortho*-palladation to give **115** (Scheme 29). Ligand exchange on **115** and **118** gave complexes **113** and **120** respectively; in turn, potassium diphenylphosphide converted these into *ortho* oxazolino phosphines **114** and **119**.[38] In an asymmetric Heck reaction, **114** was reasonably active, but the product was racemic.[47] The benzylic palladacycle (S,S_p)-**121**, derived by ligand exchange on **116**, would not react with potassium diphenylphosphide, but bromine in acetic acid converted (S,S_p)-**121** into benzylic bromide (S,S_p)-**122** (Scheme 30).[38]



Scheme 27. Synthesis of pseudo-geminally substituted oxazolinyl paracyclophanes. (i) (1) BuLi, TMEDA, (2) Ph_2CO (62–88%); (ii) (1) BuLi, (2) acetone (**99b** 82%, **99c** 78–81%, **99e** 85%); (iii) (1) BuLi, (2) DMF, (3) $NaBH_4$ (two steps: **100b** 90%, **100c** 92%, **100d** 88%); (iv) (1) BuLi, (2) Ar_2PCl (**101b** 46–71%, **101c** 82–85%, **101d** 75–82%, **101e** 68–70%, **101h** 52%, **102d** 76%, **103d** 56%, **104d** 46%, **105d** 46%); (v) (1) BuLi, (2) $PhSSO_2Ph$ (**106h** 52%); (vi) (1) BuLi, (2) CO_2, (3) H_3O^+ (**107h** 100%); (vii) (1) *t*-BuLi, (2) $B(OMe)_3$, (3) H_2O_2 (**108b** 71–75%, **108c** 71%).

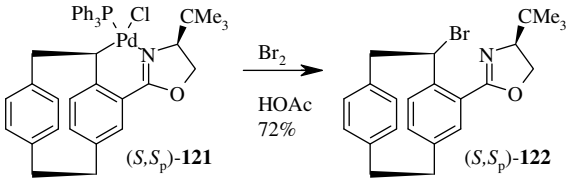


Scheme 28. Synthesis of *pseudo-ortho* oxazolino phosphines. (i) (1) *t*-BuLi, (2) XCl (**109j** 66%, **110j** 63%, **110l** 57–70%); (ii) (1) *t*-BuLi, (2) $B(OMe)_3$, (3) H_2O_2 (75%); (iii) (1) NaH, (2) BnBr (73%); (iv) (1) Me_3SiI, (2) AcOH (67–92%).

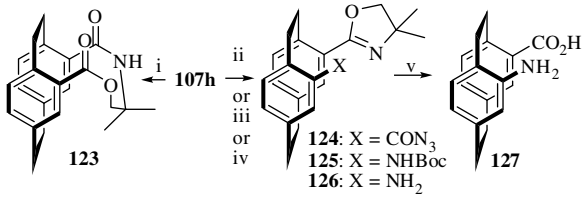


Scheme 29. Palladation of oxazolinyl paracyclophanes, and elaboration to *ortho* oxazolinyl phosphines. (i) $Pd(OAc)_2$, toluene, 80 °C (**117** y.n.s.); (ii) $Pd(OAc)_2$, HOAc, 110 °C (**116** >82%); (iii) (1) LiCl, acetone (2) PPh_3, CH_2Cl_2 (two steps: **113** 94%, **120** 90%); (iv) $KPPh_2$, toluene, rt (**114** 67%, **119** 61%).

In 2000, Pelter reported that depending on conditions, Curtius degradation of **107h** gave 17–30% yields of the bridged lactone-lactam **123** (Scheme 31), along with conventional Curtius products: acyl azide **124**, carbamate **125**, or amine **126**. By converting **107h** into its acid chloride and treating the chloride with 2-amino-2-methyl-1-propanol, **123** could be obtained as the major product.[48] From **126**, hydrolysis of the oxazoline ring gave amino acid **127** (Scheme 31).[39]

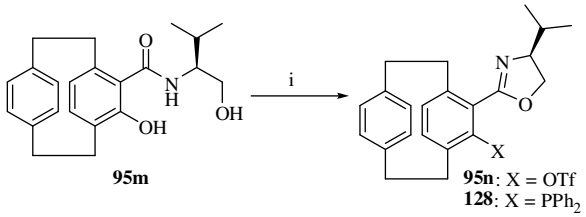


Scheme 30. Bromination of benzylic palladacycle.



Scheme 31. Curtius degradation of oxazolinyl paracyclophanecarboxylic acid. (i) (1) $SOCl_2$, (2) $H_2NCMe_2CH_2OH$, Et_3N (46%); (ii) (1) $SOCl_2$, (2) NaN_3, acetone (aq), 0 °C (**123** 17%, **124** 55%); (iii) (1) $SOCl_2$, (2) NaN_3, acetone; (3) toluene, reflux (**123** 30%, **125** 23%); (iv) (1) $(PhO)_2P(O)N_3$, DMAP; (2) *t*-BuOH, reflux (**123** 18%, **126** 58%; (v) (from **126**) HCl (aq), Δ.

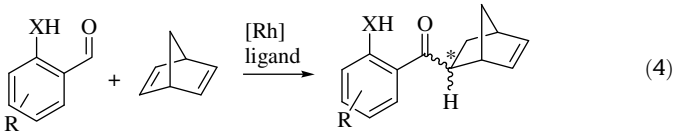
Oxazolino phosphines in the *ortho* series were prepared from the rotameric *o*-hydroxy D-valinol amides (R_p)- and (S_p)-**95m**, treatment of which with triflic anhydride led to triflation of the phenol and oxazoline closure, giving **95n**. Potassium diphenylphosphide displaced triflate to provide (R_p)- and (S_p)-**128** (Scheme 32).[40]



Scheme 32. Synthesis of *ortho* oxazolinyl phosphines. (i) (1) Tf_2O, pyridine (**95n** 73%), (2) Ph_2PK (**128** 46%).

The (R_p) and (S_p) rotamers of oxazolino phosphines **101c**, **109j**, **110jl**, and **128** were compared as ligands in Pd-catalyzed asymmetric allylic alkylations (Eq. 1). All gave complete conversion, (R_p)-**110j** and (R_p)-**110l** more slowly than the other eight. Asymmetric

inductions above 80% were observed with the three pseudo-*ortho* ligands (S_p) at the oxazoline-bearing benzene ring [(S_p)-**109j**, (S_p)-**110j**, and (S_p)-**110l**]; pseudo-geminal and *ortho* ligands gave enantiomeric excesses of 63% or lower. The absolute configuration of the new chiral center matched that of the chiral center on the oxazoline ring.[40] The *ortho* and *pseudo-geminal* oxazolino phosphines **101c** and **128** were studied as ligands in the asymmetric hydroacylation of norbornadiene (Eq. 4). Although **101c** led to high activity, **128** did not, and enantiomeric excesses were no greater than 15%.[49] The *pseudo-ortho* ligands, which gave better asymmetric induction in Pd-catalyzed allylic alkylations, have yet to be studied in hydroacylation.

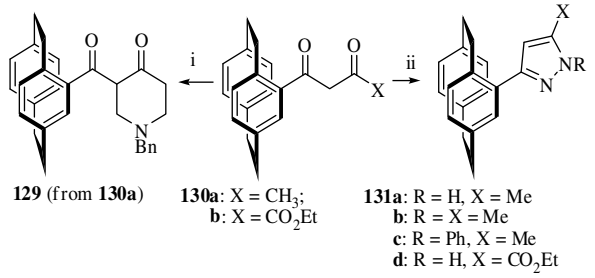


(4)

The hydroxy oxazolino ligands **95m**, **108bc**, and **111j** were studied in the addition of diethylzinc to benzaldehyde. The most active of the isopropyl-substituted ligands was **108b**, which also gave the highest asymmetric induction (78% ee). The predominant enantiomer had the opposite configuration from the oxazoline-bearing chiral plane of **108b**. The *tert*-butylated ligand **108c** gave slightly higher yield and ee than **108b**.[41]

2.11. Piperidinone, pyrazole

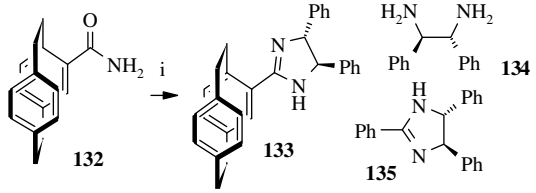
In 1992, Aly, Hopf, and co-workers reported that 4-aceto-acetyl[2.2]paracyclophane (**130a**) undergoes Mannich reaction with benzylamine and paraformaldehyde to give piperidinone **129**, and is cyclized by hydrazines to pyrazoles **131a–c**. Similarly, oxaloacetyl cyclophane **130b** is cyclized by hydrazine to pyrazolecarboxylate ester **131d** (Scheme 33). These compounds showed activity against bacteria and insect larvae.[50] Another piperidinone-bearing [2.2]paracyclophane has been prepared, and converted into a pyridine (Section 2.15).



Scheme 33. Synthesis of pyridinone- and pyrazole-bearing [2.2]paracyclophanes. (i) $BnNH_2$, $(CH_2O)_n$, HOAc (59%); (ii) $RNHNH_2$, EtOH, reflux (**131a** 87%, **131b** 83%, **131c** 82%, **131d** 79%).

2.12. Imidazoline

In 2007, Braddock described the synthesis of **133** from [2.2]paracyclophane-4-carboxamide (**132**), by imidate formation followed by condensation with (*R*,*R*)-**134** (Scheme 34). In



Scheme 34. Synthesis of imidazoline-bearing [2.2]paracyclophane. (i) (1) $Et_3O^+BF_4^-$, CH_2Cl_2, rt; (2) **134**, EtOH (30%).

bromoacetoxylations of alkenes and bromolactonizations of unsaturated acids, **133** had comparable catalytic activity to (±)-*iso*-amarine (**135**), but **133** gave no asymmetric induction.[51]

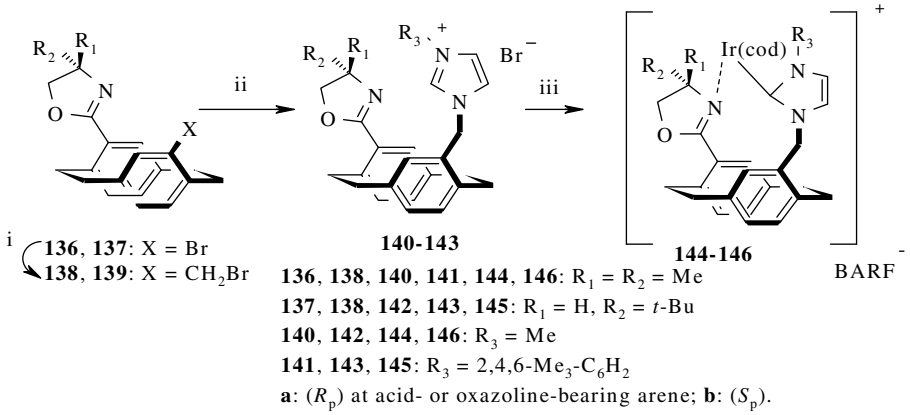
2.13. Imidazolium

It has been recently reported that the *pseudo-ortho* bromo oxazolines **136** and **137** (available in homochiral form) from **95jl** could be homologated to **138** and **139** by metalation, capture with CO_2, reduction with $LiAlH_4$, and bromination. Displacement of the bromides by *N*-alkylimidazoles provided imidazolium salts **140–143**. Deprotonation of **140–142** with *t*-BuOK followed by metalation with $[Ir(COD)Cl]_2$ and anion exchange with NaBARF furnished complexes **144–146**; the salts **143**, which combine the most hindered oxazoline and most hindered imidazolium subunits of the series, would not undergo the metalation sequence (Scheme 35). Complexes **144a**, **145ab**, and **146a** were studied as catalysts for asymmetric hydrogenation of alkenes. Complex **146a**, with planar chirality only and a large mesityl group on the imidazolium ring, gave greater conversion and higher ee than not only **144a** but **145a**, which has a stereogenic center on the oxazoline ring. Complete conversion at 25 °C required 10–50 bar H_2, and gave ee values of 9–46%. Catalysts **145ab** and **146a** all gave (*R*) product predominantly.[42,52–55]

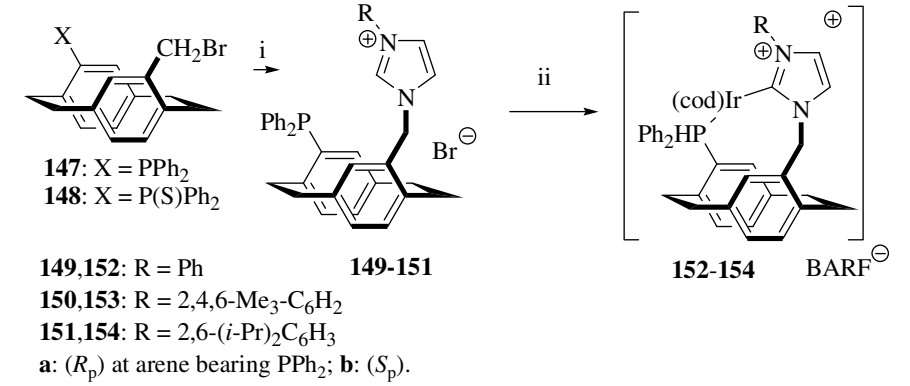
Similarly, reaction of bromomethyl phosphines **147** with imidazoles gave phosphino imidazolium salts **149–151** (Scheme 36). Synthesis of the most hindered salts **151** suffered interference from P-oxidation, but a higher-yielding route to salts **151** involved displacement on phosphine sulfide **148** followed by desulfurization with Raney nickel. Iridium complexes **152–154** were prepared as in the oxazoline series. In asymmetric hydrogenations of simple alkene substrates, catalysts **152a–154a** had similar activity; greatest asymmetric induction [up to 82% ee, (*R*) configuration] was obtained with the least hindered catalyst **152a**. In hydrogenations of α,β-enoate esters, **152a** and **153a** had higher activity than **154a**, but **154a** gave greatest asymmetric induction.[53–56]

P-Oxides of **149–151** (viz., **157–160**) were prepared by imidazole displacement of the bromomethyl phosphine oxide **155** (Scheme 37). Similar displacement of the bromomethyl methoxy paracyclophane **156** provided imidazoliums **161–163**. The imidazoliums so prepared were subjected to sodium methoxide and rhodium acetate to give rhodium carbene complexes, which were used to catalyze the addition of arylboronic acids to aldehydes. All the complexes were active catalysts, but phosphine oxides **157–160** gave greater asymmetric induction than methyl ethers **161–163**. The greatest enantiomeric excess, 29%, was obtained with **158a**. Ligands **157a** and **160a** also gave ee above 20%; all three gave the (*S*) product predominantly.[57]

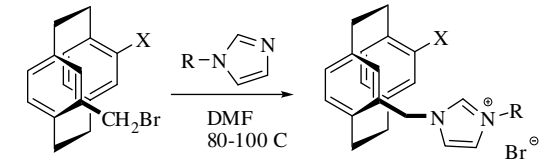
Bis(cyclophane)-imidazoliums have been prepared from the homochiral (S_p) pseudo-*ortho* alkyl amino cyclophanes **164a–c** and **9**. Reaction with glyoxal gave the corresponding diimines, which were reduced to the diamines with $NaBH_4$. Acid-catalyzed treatment with triethyl orthoformate, followed by anion exchange, furnished the C_2-symmetric (S_p,S_p) imidazoliums **166a–d** (Scheme 38). Ligands **166** were active in the rhodium-catalyzed additions of arylboronic acids and potassium aryltrifluoroborates to α,β-enones. Highest activity, and enantiomeric excesses up to 98%, were found with ligand **166c**; the new chiral center was predominantly (*S*) in all cases, matching the planar configuration of the ligand. Substrates studied included cyclic enones of five to seven members, and acylic enones of varying steric demand.[51,56,58,59] Ligands **166a**,**c**,**d** also promote the ruthenium-catalyzed asymmetric hydrosilylation of alkyl aryl ketones. Again, the best selectivity was obtained with ligand **166c** and $RuCl_2(PPh_3)_3$/AgOTf as catalyst in THF as solvent. Yields and enantiomeric excesses were above 90%, and again (*S*) alcohols predominated.[60] Similar ligands **167a–d** in the pseudo-



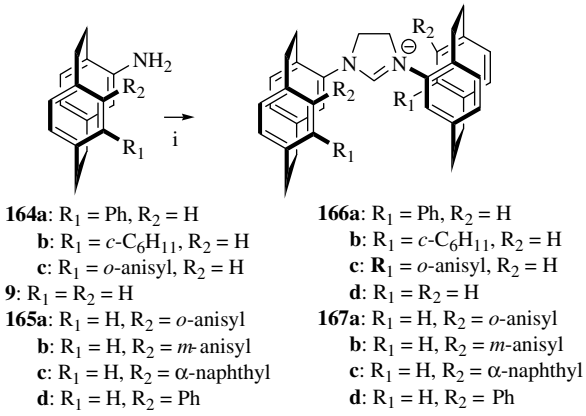
Scheme 35. Iridium carbene complexes derived from oxazolino imidazolium salts. (i) (1) *t*-BuLi, (2) CO_2, (3) $LiAlH_4$, (4) PBr_3 (**138** 68%, **139a** 36%, **139b** 46%); (ii) *N*-(R_3)-imidazole, DMF, 80° (**140** 79%, **141** 97%, **142a** 93%, **142b** 83%, **143a** 85%, **143b** 94%); (iii) (1) *t*-BuOK, (2) $[Ir(cod)Cl]_2$, (3) NaBARF (**144** 59%, **145b** 74%, **146a** 69%, **146b** 48%).



Scheme 36. Iridium carbene complexes derived from phosphino imidazolium salts. (i) (from **147**) *N*-*R*-imidazole (**149** 16%, **150** 59%, **151** 32%); (ii) (from **148**) (1) *N*-*R*-imidazole, (2) Raney nickel (**151** 32%); (iii) (1) *t*-BuOK, (2) $[Ir(cod)Cl]_2$, (3) NaBARF (**152** 54%, **153** 79%, **154** 91%).



Scheme 37. Synthesis of phosphine-oxide and methoxy imidazoliums (**157** 69%, **158** 83%, **159** 50%, **160** 35%, **161** 99%, **162** 93%, **163** 89%).

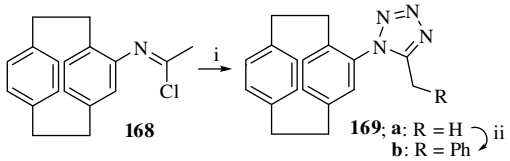


Scheme 38. Synthesis of bis(cyclophane)imidazoliums. (i) (1) OHCCHO, *n*-PrOH (aq), (2) $NaBH_4$, HCl, (3) $(EtO)_3CH$, HCO_2H, NH_4BF_4 (**166a** 62%, **166b** 50%, **166c** 51%, **166d** 61%, **167a** 81%, **167b** 80%, **167c** 72%, **167d** 91%).

geminal series have recently been prepared in analogous fashion from **165a–d**,[61] but their metal complexes have not yet been described.

2.14. Tetrazole

In 2005, Aly reported that imidoyl chloride **168** reacts with hydrazoic acid to give tetrazole **169a** (Scheme 39). In turn, reaction with benzyne converted **169a** into **169b**.[62]



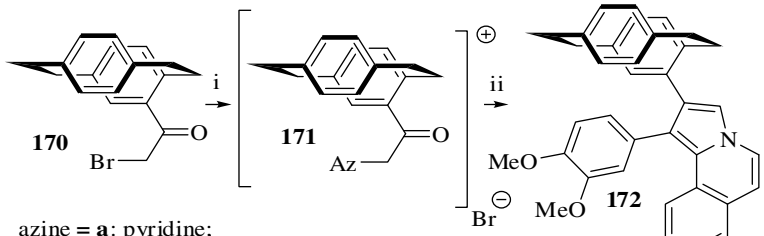
Scheme 39. Preparation of tetrazolyl paracyclophanes. (i) HN_3, benzene, reflux (>85%); (ii) *o*-$(HO_2C)C_6H_4(N_2^+)$, MeCN, reflux (78%).

2.15. Pyridine, benzo[g]indolizine, quinoline, benzo[*h*]quinoline, furoquinoline

As mentioned above (Section 2.4; Scheme 6), nitrone **29** reacts with dibenzoylethene to furnish (2-pyridyl)paracyclophane **25**.[11]

The result seems not to be general: other dipolarophiles react with **29** to give a variety of products containing five-membered aza-cycles, but no other pyridines have been produced from **29**.[12]

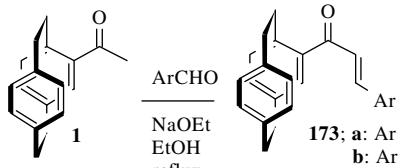
Soldatenkov's group has studied numerous paracyclophanes bearing pyridines and tetrahydropyridines. In 1994 they reported that 4-(bromoacetyl)[2.2]-paracyclophane (**170**) reacts with a variety of azines to furnish the corresponding azinium bromides **171a–n** (Scheme 40). Chichibabin cyclization of **171n** provided the paracyclophane-bearing benzo[*g*]indolizine **172**.[63]



azine = **a**: pyridine;
b: 2-methylpyridine; **c**: 3-methylpyridine;
d: 4-methylpyridine; **e**: 2-methyl-5-ethylpyridine;
f: 2-(hydroxyethyl)pyridine; **g**: 2,5-Me_2-4-benzylpyridine;
h: 2,5-Me_2-4-(*p*-$O_2NC_6H_4CH_2$)pyridine**; i:** quinoline;
j: isoquinoline; **k**: papaverine; **l**: acridine; **m**: 9-H_2N-acridine; **n**: pyrazine

Scheme 40. Preparation and cyclization of paracyclophane-bearing azinium salts. (i) Azine, acetone, reflux (**171a** 67%, **171b** 60%, **171c** 55%, **171d** 63%, **171e** 70%, **171f** 90%, **171g** 72%, **171h** 82%, **171i** 65%, **171j** 64%, **171k** 70%, **171l** 56%, **171m** 49%, **171n** 58%); (ii) (from **171n**) K_2CO_3, acetone/MeCN, 56 °C (80%).

Reactions of **1** with 2-, 3-, and 4-pyridine-carboxaldehydes gave the corresponding aldol products (**173**: Scheme 41). Benzaldehyde and some substituted analogues reacted similarly. None of these compounds showed antibacterial activity, and their fungicidal activity was low.[64]

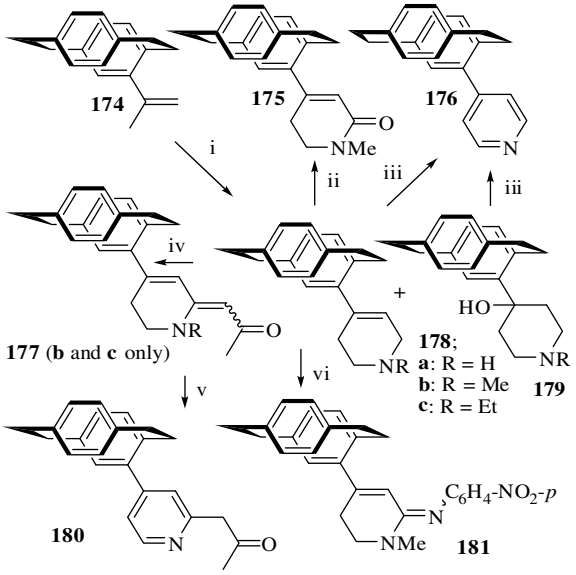


173; **a**: Ar = 2-pyridyl (43%)
b: Ar = 3-pyridyl (90%)
c: Ar = 4-pyridyl (70%)

Scheme 41. Aldol condensations of acetyl[2.2]paracyclophane with arenecarbaldehydes.

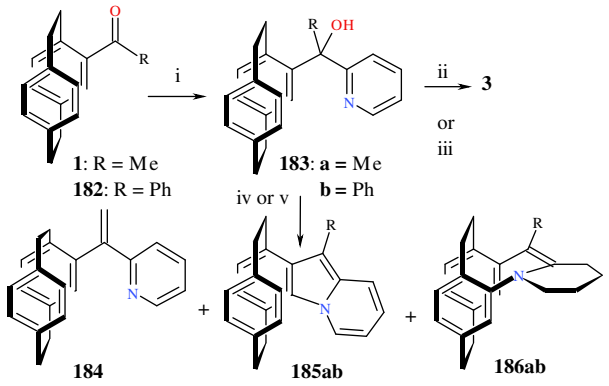
Condensation of **174** with formaldehyde and amines provided **178a–c** as mixtures with tetrahydropyridines **179a–c** (Scheme 42).[65–69] The latter, in turn, underwent acid-promoted dehydration to **178a–c**. Heating of **178a** or **178b** with elemental sulfur at 180–200 °C gave 4-(4-pyridyl)-[2.2]paracyclophane (**176**) in up to 10% yield along with tar, but heating of **178b** or **178c** with sulfur at 140 °C raised the yield of **176** to 60%.[65] The authors conceived systems **178** as tetrahydropyridines bearing [2.2]paracyclophane as a bulky substituent, to study their permanganate oxidations;[66] reaction of **178b** with $KMnO_4$ in aqueous MeCN at 50 °C gave tetrahydropyridin-2-one **175** in 50% yield.[65] Oxidation of **178b** or **178c** with $KMnO_4$ in acetone led to the respective condensation products **177bc**, both as *E*/*Z* mixtures.[67] A crystal structure of (*E*)-**177b** has been reported.[68] Other methyl ketones and nitromethane were condensed with 4-phenyltetrahydropyridine, but these reactions have not yet been described in the cyclophane series. Aromatization of either **177b** or **177c** with sulfur at 140 °C furnished pyridine **180**.[67] Oxidation of **178b** with $KMnO_4$ in aqueous acetonitrile in the presence of *p*-nitroaniline provided imine **181**, presumably via **175** as intermediate.[69]

Reaction of **1** or **182** with 2-pyridyllithium gave paracyclophanyl pyridyl carbinols **183a** and **183b**, respectively; **183a** and **183b** could also be obtained by bromine–lithium exchange on 4-bromo[2.2]-paracyclophane (**3**) followed by capture with 2-acetylpyridine or 2-benzoylpyridine, but in much lower yields (Scheme 43).[70] Crystal structures were determined, of **183a** itself and the CuCl complex of **183b**. Heating of **183a** in formic acid gave a mixture of alkene **184** (26% yield), indolopyridine **185a** (16%), and an inseparable 2:1 mixture (16%) of **185a** and the bridged polycycle **186a**.[70a] Direct dehydration of **183b** to an alkene like **184** being impossible, heating of **183b** in formic acid gave indolizine **185b** (25% yield) and bridged polycycle **186b** (35%).[70b]

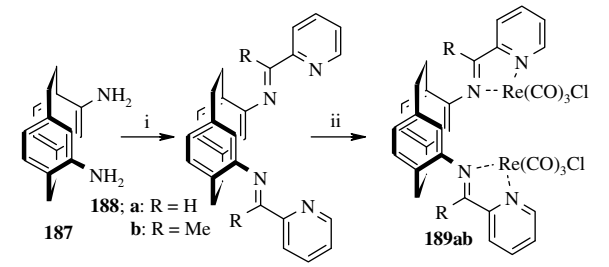


Scheme 42. Synthesis and oxidation of tetrahydropyridyl paracyclophanes. (i) CH_2O, RNH_2, H^+, H_2O, 80–90 °C (**178a**+**179a** 35%, **178b** 15%+**179b** 30%, **178c** 50%+**179c**); (ii) (from **178b**) $KMnO_4$, MeCN (aq) (50%); (iii) sulfur, (from **178b** at 140 °C, 60%, from **179a** at 180–200 °C, 10%); (iv) $KMnO_4$, acetone (aq) (**177b** 75%, **177c** 42%); (v) (from **177b** or **177c**) sulfur, 140 °C (30%); (vi) *p*-O_2N-$C_6H_4NH_2$, $KMnO_4$, MeCN (aq), rt (29%).

In 2004, Connick reported that reaction of pseudo-*ortho*-diamino[2.2]paracyclophane (**187**) with 2-pyridine-carboxaldehyde or 2-acetylpyridine gave imines **188** (Scheme 44). A crystal structure of **188a** was described. Reaction of **188ab** with $Re(CO)_5Cl$ yields the bis[$Re(CO)_3Cl$] complexes **189ab**, which exist as 1:1 mixtures of their racemic and *meso* isomers, and are non-luminescent unlike a model bis[$Re(CO)_3Cl$] complex derived from *p*-phenylenediamine, or a mono[$Re(CO)_3Cl$] complex derived from *p*-toluidine. Presumably either nonradiative excited-state relaxation is relatively fast in **189ab**, or radiative relaxation is slow. Voltammograms of **189ab** show two closely spaced reversible reductions, consistent with consecutive one-electron reductions of weakly interacting redox centers. By contrast, the model complex derived from *p*-phenylenediamine shows two well-separated reductions, denoting stronger interaction between the carboxaldimine groups.[71]

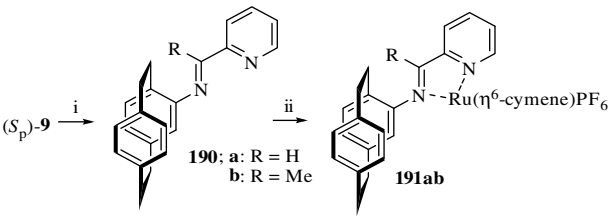


Scheme 43. Synthesis and acid-catalyzed reactions of paracyclophanyl pyridyl carbinols. (i) 2-PyLi (**183a** from **1**: 45%; **183b** from **182**: 62%); (ii) (1) *n*-BuLi, (2) 2-AcPy (**183a** 5%); (iii) (1) *n*-BuLi, (2) 2-BzPy (**183b** 8%); (iv) (from **183a**) HCO_2H (**184** 26%, **185a** 16%, **185a**+**186a** 16%); (v) (from **183b**) HCO_2H (**185b** 25%, **186b** 35%).



Scheme 44. Binuclear Re^{I} complexes with bridging paracyclophane-diimine ligands. (i) (2-Py)CHO or 2-AcPy, EtOH, 60 °C (**188a** 84%, **188b** 23%); (ii) $Re(CO)_5Cl$, PhH, 60 °C (**189a** 69%, **189b** 50%).

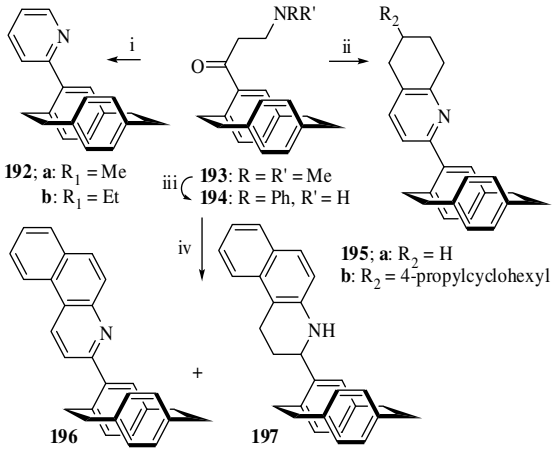
Similarly, the Perugia group reports the reaction of (S_p)-**9** with 2-pyridinecarboxaldehyde or 2-acetylpyridine to give **190a** or **190b**, respectively (Scheme 45). Reaction of **190ab** with [Ru(η^6-cymene)Cl(μ-Cl)]$_2$ then furnishes complexes **191ab** as mixtures of their (S_{Ru},S_p) and (R_{Ru},S_p) diastereomers. These are configurationally stable at the ruthenium center; the cymene orientation depends on the diastereomer, and is governed by minimum steric repulsion between the cymene and the *N*,*N*-ligand. Catalytic application of these complexes, while hinted at in the paper's introduction, has not yet been reported.[72]



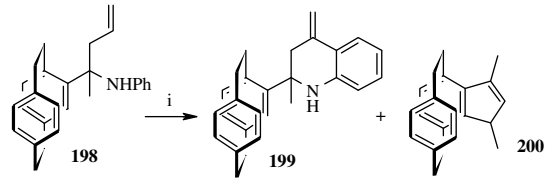
Scheme 45. Ru^{I} complexes with one paracyclophane-diimine ligand. (i) (2-Py)CHO (to **190a**) or 2-AcPy (to **190b**), HCO_2H, MeOH, rt (**190a** 58%, **190b** 58%); (ii) (1) [Ru(η^6-cymene)Cl(μ-Cl)]$_2$, MeOH, rt, (2) NH_4PF_6, MeOH, rt (**191a** 75%, **1961** 83%).

Condensations of **193** with aliphatic aldehydes in the presence of hydroxylamine furnished paracyclophanyl pyridines **192ab**, while condensations with cyclohexanones furnished quinolines **195ab** (Scheme 46). Reaction of **193** with aniline led only to transamination, giving **194**, but **193** with α-naphthylamine provided benzo[*h*]quinoline **196** and tetrahydrobenzo[*h*]quinoline **197**.[73]

Acid-promoted cyclization of allyl paracyclophanyl aniline **198** provided tetrahydroquinolinyl paracyclophane **199** and cyclopentenoparacyclophane **200** (Scheme 47).[74]

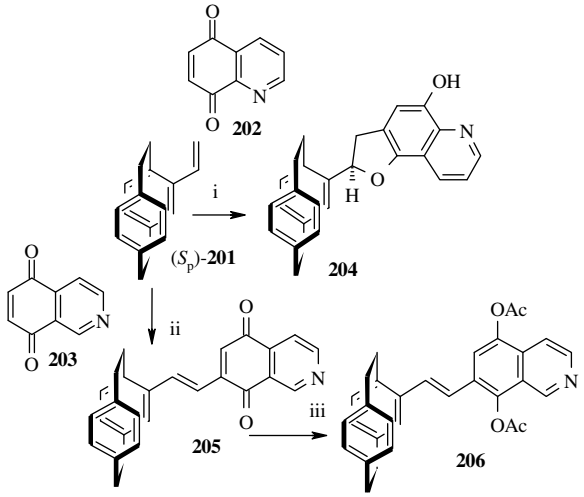


Scheme 46. (1) R_1CH_2CHO, dioxane, NaOAc, hydroquinone, 100–102 °C, (2) NH_2OH, H_2O, 90–92 °C (**192a** 15%, **192b** 25%); (ii) (1) 4-(R_2)-cyclohexanone, dioxane, NaOAc, hydroquinone, 100–102 °C, (2) NH_2OH, H_2O, 90–92 °C (**195a** 18%, **195b** 40%); (iii) $PhNH_2$, reflux (49%); (iv) (from **193**) α-naphthylamine, concd HCl, 200 °C (**196** 18%, **197** 5%).



Scheme 47. Acid-promoted cyclization of allyl paracyclophanyl aniline. (i) $CHCl_3$/H_2SO_4 (2:1), 60 °C (**199** 15%, **200** 30%).

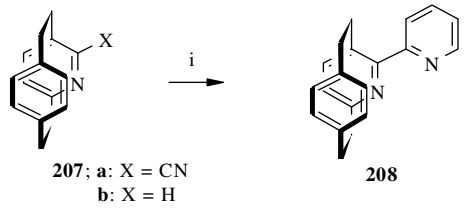
In 2003, Minuti et al. reported that the behavior of (S_p)-4-vinyl[2.2]paracyclophane (**201**) towards quinoline-5,8-dione (**202**) and isoquinoline-5,8-dione (**203**) varies greatly with the conditions. In toluene at 120 °C under atmospheric pressure and catalysis by $BF_3 \cdot Et_2O$, **201** and **202** gave recovered starting materials, but **201** and **203** furnished the quinolinyl cyclophane **205**, the reductive acetylation of which then gave **206** (Scheme 48). At a pressure of 6 kbar without Lewis acid, both quinones decomposed, but at 6 kbar with $BF_3 \cdot Et_2O$, **201** and **203** gave a complex mixture from which no product could be isolated, while **201** and **202** led cleanly to furoquinoline derivative **204**.[75]



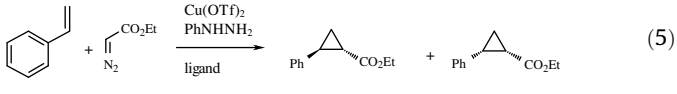
Scheme 48. Reactions of 4-vinylparacyclophane with heterocyclic quinones. (i) **202**, $BF_3 \cdot Et_2O$, 6 kbar, Et_2O, CH_2Cl_2, 50 °C (53%); (ii) **203**, $BF_3 \cdot Et_2O$, toluene, 120 °C (30%); (iii) Zn, Ac_2O (80%).

Vögtle's group has prepared an aza analogue of 4-(2-pyridyl)-paracyclophane. Cobalt-catalyzed reaction of 13-cyano[2]para-

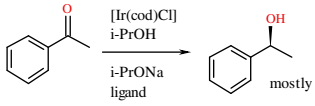
cyclo[2](2,5)-pyridinophane (**207a**) with excess acetylene gave the planar-chiral bipyridine **208**, which was resolved by chiral HPLC (Scheme 49). By analogy with the CD spectra of **207b**, (−)-**208** was assigned as (R_p). In Cu^I-catalyzed cyclopropanation of styrene with ethyl diazoacetate (Eq. 5), use of ligand **208** led to a mixture of cis-product (47% yield, 10% ee) and trans-product (25% yield, 23% ee). In Ir^I-catalyzed transfer hydrogenation of acetophenone (Eq. 6), **208** led to (*S*)-1-phenylethanol (91% yield, 31% ee).[76]



Scheme 49. Preparation of planar-chiral bipyridine. (i) (from **207a**) acetylene (1.5 bar), CoCp(cod) (2 equiv), toluene, 120 °C, 20 h; 23%.



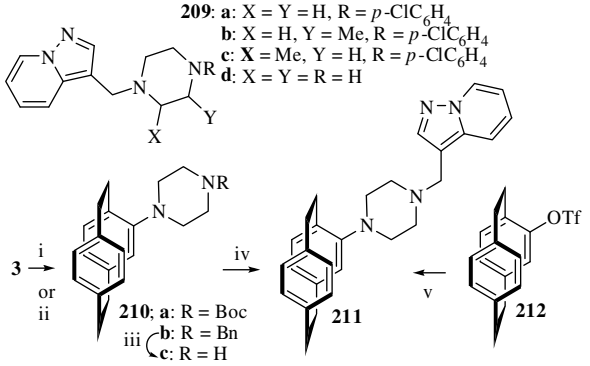
(5)



(6)

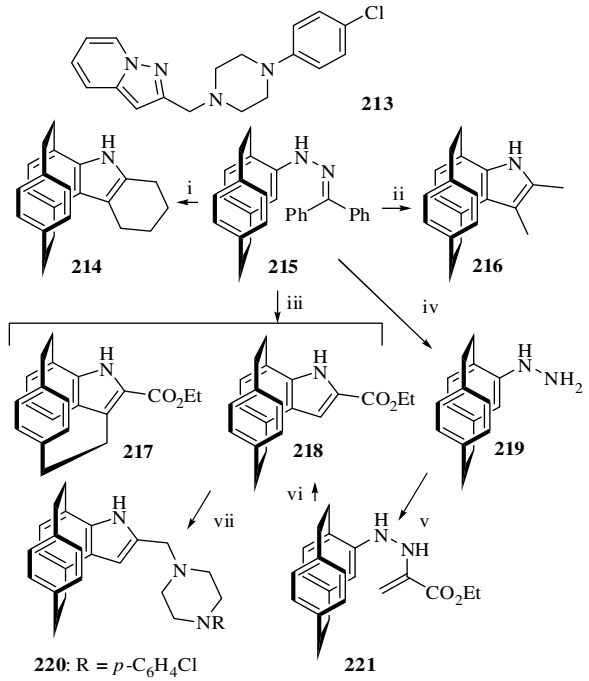
2.16. Piperazine, pyrazolo[1,5-*a*]pyridine

Gmeiner has studied various bioisosters of dopamine receptor ligands. To produce an analogue of the D4 ligand FAUC113 (**209a**) wherein the *p*-chlorophenyl group is replaced with a [2.2]paracyclophane moiety, (±)-**3** was coupled with *N*-Boc- or *N*-benzylpiperazine under catalysis by potassium *tert*-butoxide (palladium-free conditions) to provide **210a** or **210b**, respectively, the latter in better yield. Removal of the *N*-benzyl group from **210b** required conversion into a carbamate followed by acid-catalyzed release of the secondary amine, to provide the parent piperazinyl paracyclophane **210c**. Mannich coupling of **210c** with pyrazolo[1,5-*a*]pyridine furnished (±)-**211**. Enantiopure (R_p)- and (S_p)-**211** were obtained by Stille coupling of triflates (R_p)- and (S_p)-**212** [(S_p) shown] with amine **209d** (Scheme 50). Compounds (R_p)- and (S_p)-**212** were evaluated in vitro for ability to displace [^{3}H]spiperone from some cloned human dopamine receptors. They had lower affinity for receptor D4, but higher affinity for D2 and D3, than lead compound **209a** or analogues **209bc**.[77]



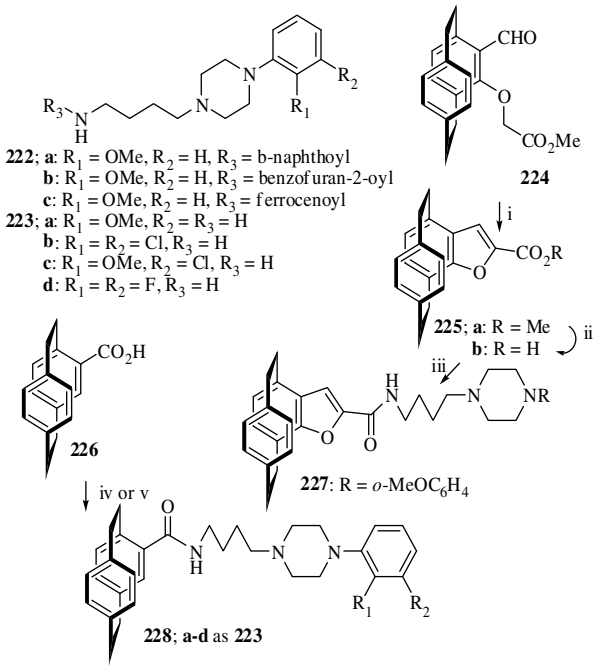
Scheme 50. Synthesis of planar-chiral pyrazolo[1,5-*a*]pyridines. (i) *N*-Boc-piperazine, *t*-BuOK, toluene, 130 °C (**210a** 16%); (ii) *N*-Bn-piperazine, *t*-BuOK, toluene, 130 °C (**210b** 64%); (iii) (1) $ClCO_2Me$, (2) concd HCl (65%); (iv) pyrazolo[1,5-*a*]pyridine, CH_2O, HOAc, CH_2Cl_2 (81%); (v) **209d**, $Pd_2(dba)_3$, dppf, *t*-BuONa, toluene, 100 °C, 24 h (42%).

To replace the pyrazolo[1,5-*a*]pyridine subunit of FAUC213 (**213**) with [2](4,7)indolo[2]paracyclophane, a synthesis of the indolo-paracyclophane structure was approached using Buchwald's variant of the Fischer indole synthesis (Scheme 51). One-pot reaction of hydrazone **215** with cyclohexanone and TsOH provided **214**; under the same conditions, **215** and butanone gave **216**. However, **215** and ethyl pyruvate gave a mixture of the desired Fischer product **218** and the rearranged isomer **217**. Stepwise reaction suppressed rearrangement: first, the hydrazone was deprotected in the presence of ethylene glycol, which ketalizes the released benzophenone; second, the free hydrazine **219** was condensed with ethyl pyruvate to furnish **221**; finally, cyclization of **221** led cleanly to **218**. With **218** in hand, its reductive amination with (*p*-chlorophenyl)piperazine provided test compound **220**, which proved to display strong and selective affinity for the dopamine D4 receptor subtype.[78] The same stepwise reaction sequence applied to (R_p)- and (S_p)-**215** led respectively to (R_p)- and (S_p)-**220**, of which (R_p)-**220** showed significantly higher affinity for all receptor subtypes investigated.[79]



Scheme 51. (i) Cyclohexanone, TsOH, EtOH, reflux, 18 h (34%); (ii) Butanone, TsOH, EtOH, reflux, 18 h (23%); (iii) $AcCO_2Et$, TsOH (**217** 23%, **218** 23%); (iv) $HOCH_2CH_2OH$, TsOH; (v) $AcCO_2Et$ (61% from **213**); (vi) TsOH, benzene, reflux, 45 min (**218** 45%); (vii) *N*-(*p*-ClC_6H_4)-piperazine, $LiAlH_4$, THF (53%).

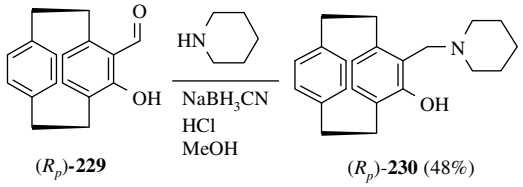
Starting in concept with the D3 receptor ligand BP897 (**222a**) and its analogues **222bc**, replacement of the aromatic portions of their arenecarboxamide subunits leads to structures **227** and **228** (Scheme 52). Internal aldol condensation of **224** gave benzofuran-carboxylate ester **225a**, which was saponified to acid **225b**. Reaction of **225b** with amine **223a** under standard peptide-coupling conditions then furnished **227**. Similarly, coupling of [2.2]paracyclophane-4-carboxylic acid (**226**) with **223a–d** gave the corresponding amides **228a–d**, and the enantiopure acids (R_p)- and (S_p)-**226** gave (R_p)- and (S_p)-**228a** respectively. Compounds **227** and **228** all bound preferentially to the dopamine D3 receptor subtype; the most promising compound was **228a**, the (R_p) enantiomer of which bound almost 100-fold more strongly than **227** and 10-fold more strongly than the original lead compound **222a**. In a mitogenesis assay, compounds **228** showed D3 antagonist activity, (R_p)-**228a** again being the strongest.[80]



Scheme 52. Cyclophane analogues of BP897. (i) KH, NMP (59%); (ii) NaOH, MeOH, THF (80%); (iii) **223a**, HATU, HOAt, DIPEA, DMF, CH_2Cl_2 (81%); (iv) **223a** or **223b**, HATU, DIPEA, NMP (**228a** 94%, **228b** 94%); (v) **223c** or **223d**, TBTU, DIPEA, DMF, CH_2Cl_2 (**228c** 91%, **228d** 64%).

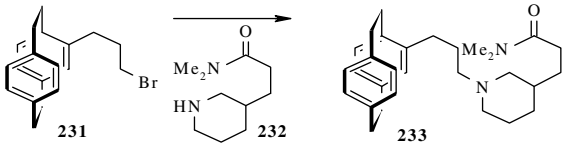
2.17. Piperidine

In 2001, Bräse reported that reductive amination of (R_p)-5-hydroxy[2.2]paracyclophane-4-carbaldehyde (**229**) with piperidine gave (R_p)-**230**, which was acid sensitive and decomposed on silica (Scheme 53). Decomposition was attributed to protonation of the tertiary amine, followed by elimination. An analytical sample of (R_p)-**230** was obtained by chromatography on alumina.[81]



Scheme 53. Preparation of hydroxy piperidinyl [2.2]paracyclophane.

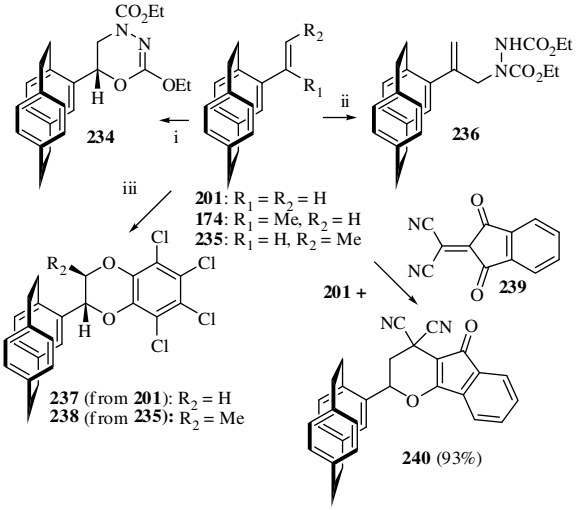
In 1991, Psiorz and Trach described the condensation of 4-(3-bromopropyl)[2.2]paracyclophane (**231**) with *N*,*N*-dimethyl-3-(3-piperidyl)propionamide (**232**) to provide the displacement product **233** (Scheme 54), which gave 48% reduction of blood pressure in rats at 1 mg/kg iv.[82]



Scheme 54. Preparation of piperidinyl [2.2]paracyclophane cardiovascular agent.

2.18. 1,3,4-Oxadiazine, benzodioxane, tetrahydropyrano[*b*]indan-2-one

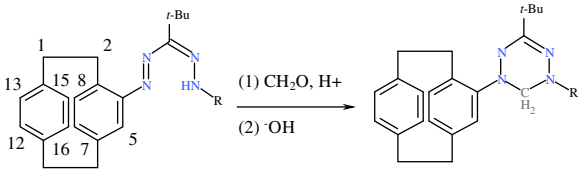
In 2006, Aly and Hopf et al. described cycloadditions of alkenyl[2.2]paracyclophanes. Reaction of **201** with diethyl azodicarboxylate led to [4+2] cycloaddition, **201** acting as dienophile, to give oxadiazine **234** as a single regio- and stereoisomer (Scheme 55). The energetics of several reaction pathways seem to be finely balanced: reaction of 4-isopropenyl[2.2]paracyclophane (**174**) led to ene reaction, giving **236**. With tetrachloro-*o*-benzoquinone (**241**), **201** again acts as dienophile, to provide **237**. The stereochemical course of this cycloaddition is illuminated by the reaction between **241** and 4-[(*E*)-1-propenyl][2.2]paracyclophane (**235**), which gives adduct **238**. The structure of compound dioxane molecules was to have the *E* (*trans*) geometry across the single bond C2′–C3′. The structure of **238** was confirmed crystallographically. In a similar fashion, **201** reacts with **239** to furnish adduct **240**. With other partners, **201** acts as a diene (Section 3.7).[83]



Scheme 55. Vinyl[2.2]paracyclophane as a [4+2] dienophile. (i) **201**+DEAD (18%); (ii) **174**+DEAD (30%); (iii) **241** (**237** 62%, **238** 65%).

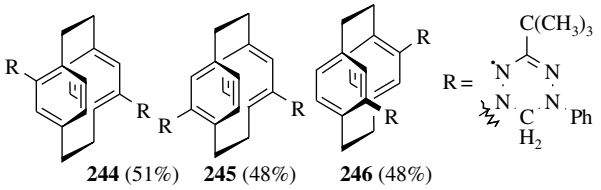
2.19. Verdazyl

Between 1977 and 1981, Neugebauer described studies of verdazyl-bearing [2.2]paracyclophanes. The verdazyl group was used as an intramolecular spin probe, to study transannular interactions between the verdazyl-substituted benzene ring, and the other benzene ring. To interpret the NMR data required assigning the proton hyperfine coupling constants, which was done using deuterated derivatives. Cyclization of formazans **242a–f** with formaldehyde, followed by deprotonation, gave verdazyls **243a–f** (Scheme 56). In di-*tert*-butylnitroxide as solvent, the ^2H and ^1H NMR spectra of **243a–f** were well enough resolved for interpretation. In **243c** and **243d**, paramagnetic shifts of the deuterons in the 'opposite' benzene ring (D-1,10,12,13,15,16) were small (<|3| ppm), indicating no substantial transannular interaction of the unpaired electron with the opposite benzene ring.[84]



Scheme 56. Verdazyl-bearing [2.2]paracyclophanes. **243a** 70%, other yields are not stated.[84]

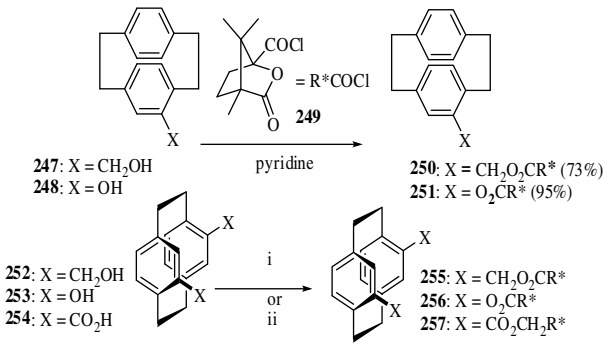
Earlier, Neugebauer's group had observed that biverdazyls linked by oligo(*p*-phenylene) bridges have both a singlet ground state and an adjacent triplet that is thermally populated at room temperature.[85] To explore the possibility of similar electronic coupling in a transannular sense, the [2.2]paracyclophane-linked biverdazyls **244**–**246** were prepared from the corresponding bisformazans (Scheme 57). These, too, showed no substantial transannular interactions. Attempts to cyclize a pseudo-geminal bisformazan, which would have given a biverdazyl with the verdazyl rings held essentially face-to-face, unfortunately failed.[86]



Scheme 57. [2.2]Paracyclophane-linked biverdazyls. Yields shown are for last step per Scheme 56.

2.20. Camphanate

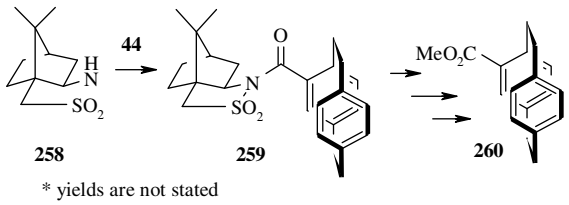
Camphanate esters have been used by several groups to either resolve or determine absolute configuration of paracyclophane-derived alcohols. The first of these reports was by Tochtermann, who esterified (+)- and (−)-[2.2]paracyclophane-4-methanol (**247**) with (1*S*)-camphanoyl chloride (**249**) to furnish diastereomers **250** (Scheme 58). An X-ray crystal structure revealed the ester from (+)-**247** to have structure **250** with (S_p) configuration,[87] for which the authors use the older term (*M*).[88] Thus, (+)-**247** is (S_p)-**247**; since alcohols **247** were made by reduction of the corresponding acids **226**, those absolute configurations followed also.[87] Likewise, Rozenberg and Hopf esterified racemic **248** with **249** to give the separable diastereomers **251**. Crystal structures established the absolute configurations of **251**, and thus also those of **248**.[89] Similarly, Jones esterified (+)-**252** with **248** to give diester **255**, the crystal structure of which revealed (+)-**252** to have configuration (S_p,S_p) as shown.[90] Alcohols **247** and **252** had been resolved as the acids, before camphanoylation; Jiang has resolved camphanate-bearing [2.2]paracyclophanes directly. Esterification of (±)-**253** with **249** gave the separable diesters **256**. After separation, $LiAlH_4$ reduction released the separated alcohols **253** in 44–45% yields and 99.8–99.9% ee.[91] In analogous fashion, (±)-**254** was resolved by conversion to the racemic acid chloride followed by esterification with (1*S*)-camphanyl alcohol. The resulting esters **257** were separated, then saponified to the separated acids **254** in 35% yield each from racemic acid and 97–99% ee.[92]



Scheme 58. Resolution of paracyclophane-derived alcohols via camphanate esters. (i) (from **252** or **253**) **249**, pyridine (**255** y.n.s., **256** 91%); (ii) (from **254**) (1) $SOCl_2$, (2) R^*CH_2OH, pyridine (**257** 55%).

2.21. Camphorsultam

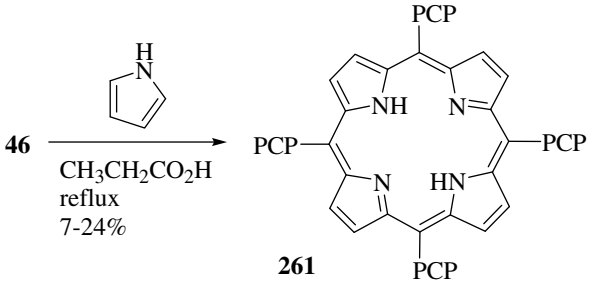
In 1993, Harada described (1*S*,2*R*,4*S*)-camphorsultam (**258**) as an auxiliary for optical resolution of carboxylic acids by HPLC, and for crystallographic determination of their absolute configuration. Reaction of **258** with (±)-**44** gave the diastereomeric amides **259**, which were separated by HPLC. Crystallography established the planar configuration of one amide as (S_p) and the other as (R_p), as expected. Cleavage of (R_p)-**259** by $LiAlH_4$ reduction, followed by Jones oxidation to the acid and conversion into the methyl ester using CH_2N_2, gave (R_p)-(−)-**260**; the same sequence correlated (S_p)-**259** with (S_p)-(+)-**260** (Scheme 59).[93] These assignments confirm those made earlier by Tochtermann, using camphanate esters (Section 2.20).



Scheme 59. Resolution of [2.2]paracyclophane-4-carboxylic acid using camphorsultam.

2.22. Porphine

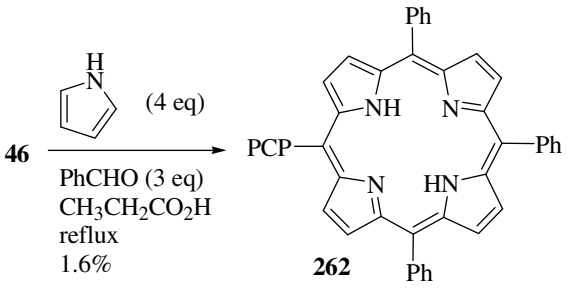
Porphyrins bearing [2.2]paracyclophanyl groups have been studied in some detail, mostly by Czuchajowski's group. Reaction of (±)-**46** with pyrrole in refluxing propionic acid furnished *meso*-tetrakis([2.2]paracyclophanyl)porphyrin (**261**; Scheme 60).[94,95] In the UV–vis spectrum of **261**, all bands are bathochromically shifted by 16–25 nm versus those of tetraphenylporphyrin.[94] Given that each paracyclophan-4-yl group lacks a plane of symmetry, atropisomers are possible; in addition, each paracyclophanyl group can be (R_p) or (S_p), rendering the stereochemistry of **261** exceedingly complex.[95,96] Two atropisomers of **261** were isolated by TLC, and two others observed but not isolated;[96] correlation of R_f values with calculated dipole moments led to assignment of the isolated isomers as UUUD and UUDD forms (in more conventional porphyrin terminology, ααaβ and ααββ, respectively). The planar-chiral composition of these isomers was unknown. Room-temperature synthesis under Lindsey's conditions gave a 28% yield;[95] high-temperature synthesis gave more of the higher-energy UUUD isomer.[95,96]



Scheme 60. Preparation of *meso*-tetrakis(paracyclophanyl)-porphine. PCP=[2.2]paracyclophan-4-yl.

For structural simplicity, this group prepared *meso*-paracyclophanyltriphenylporphyrin (**262**), by mixed condensation of **46** with benzaldehyde and pyrrole in a 1:3:4 molar ratio (Scheme 61). In the UV–vis spectrum of **262**, all bands are bathochromically shifted versus those of tetraphenylporphyrin, but by only 5–7 nm,[97]

as compared to 16–25 nm for **261**.[94] Cyclic voltammograms of **262** reveal consecutive reduction steps to anion radical **262**$^{\bullet-}$ and dianion **262**$^{2-}$, at −1.24 and −1.53 V vs SCE.[97] Reductions of **261** occur at −1.27 and −1.65 V.[98] For electrode oxidation, **262** exhibits three oxidation waves, the first at $E_{1/2}$=0.95 V. This potential is lower than that (1.05 V) of tetraphenylporphyrin, showing that the [2.2]paracyclo-phanyl group facilitates oxidation.[97] In **261**, $E_{1/2}$ for the first oxidation is decreased further, to 0.52 V. When the potential was scanned from 0.0 to 1.65 V, four oxidation processes were observed: at 0.52, 0.88, 1.30, and 1.46 V.[98] The first two peaks were attributed to formation of **261**$^{\bullet+}$ and **261**$^{2+}$, respectively, and the third and fourth to oxidation of the paracyclophanyl groups.[98] Oxidation of the second paracyclophanyl group led to formation of polymeric films,[99] which was also observed on multi-scan voltammetry.[98] The Fe^{III}Cl complex of **261** formed films similarly, which showed catalytic activity in the reduction of dioxygen.[99] Oxidative polymerization of **262** is thought to involve a semiquinoid or quinoid arrangement of bonds in the paracyclophanyl group, followed by polymerization through benzylic positions. The specific conductivity of a dry, polymeric film of **262** is 5–20 Ω^{-1} cm^{-1}, and an electrode bearing such a film efficiently catalyzes the oxidation of either water or hydrazine.[99b,100]



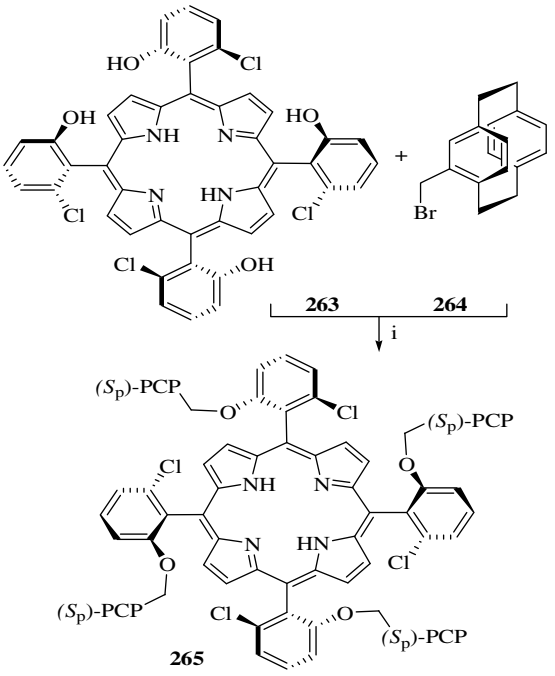
Scheme 61. Preparation of *meso*-paracyclophanyltriphenyl-porphyrin.

The Co^{II} complexes of **261** and **262** were prepared from the free bases and Co(OAc)$_2$. Complex **262**–Co^{II} undergoes reversible reduction at −0.90 V followed by irreversible reduction at −1.26 V. The first potential is typical for one-electron reduction of Co^{II} porphyrins; the second process is assigned as reduction of **262**–Co^{I} to the anion radical. Complex **261**–Co^{II} undergoes only reduction of Co^{II} to Co^{I}, at −0.93 V. In cyclic voltammetry of **262**–Co^{II}, the first two oxidation peaks are observed at 0.83 and 0.95 V and are reversible. The first is ascribed to the Co$^{II/III}$ couple and the second to formation of a cation radical. Further oxidation to the dication, at 1.20 V, is only quasi-reversible and is followed by deposition of a conductive film on the electrode. Voltammograms of **261**–Co^{II} show three ill-defined peaks at 0.75, 0.92, and 1.14 V, all irreversible. Thus, all oxidations are more facile with four paracyclophanyl groups than with only one, and polymerization is facilitated also.[101]

Complexes of **261** with Mn^{II}, Fe^{II}, and Ni^{II} were prepared, and compared to the free base and Co^{II} complex. The same pattern of three oxidations, described above for **261**–Co^{II}, was also observed for the other three complexes. The Ni^{II} complex was oxidized at the lowest potentials for all three oxidations (0.77, 0.96, and 1.18 V), and the Fe^{II} complex at the highest (1.00, 1.28, and 1.37 V). Continuous-scan cyclic voltammetry created polymeric films of all four complexes, and all the films catalyzed the electroreduction of dioxygen in acidic or basic media.[99b,102]

Quici has shown that the isomeric purity of **261** can be greatly improved by making it from homochiral **46**: if all four paracyclophanyl groups have the same planar chirality, the number of possible isomers drops to only four (αααα, ααaβ, ααββ, αβαβ). In this way, (R_p)- and (S_p)-**261** were prepared, where the planar-chiral sense describes all four paracyclophanyl groups, as inseparable 4:2.5:1 mixtures of their ααaβ, ααββ, and αβαβ atropisomers. These porphyrins were converted into their Mn^{III}Cl complexes, and studied as catalysts for the asymmetric epoxidation of alkenes by hypochlorite. Conjugated (*Z*)-alkenes were epoxidized in 31–73% yields and 22–31% ee; non-conjugated or (*E*)-alkenes were not epoxidized.[103]

That study could not address the catalytic activity or enantioselectivity of individual atropisomers. Assembly of an atropisomerically pure, chiral porphyrin required a porphyrin scaffold the atropisomers of which are configurationally stable. Reaction of αβαβ-**263** with (S_p)-4-bromomethyl[2.2]paracyclophane (**264**) and K_2CO_3 furnished **265** (Scheme 62). The Mn^{III}–Cl complex of **265** catalyzed the hypochlorite epoxidations of conjugated or isolated alkenes, and the iodosobenzene epoxidation of styrene, but all the products were racemic, and the catalyst was inactive in epoxidations by hydrogen peroxide.[104] The catalytic activity or enantioselectivity of atropisomers other than αβαβ remains unknown. One salutes the elegance of this work, although its practical results were disappointing.

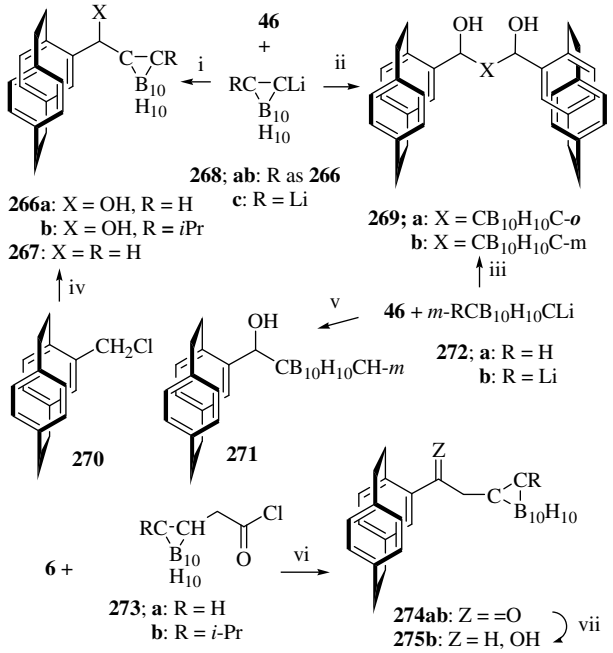


Scheme 62. Synthesis of atropisomerically pure, chiral porphyrin. PCP=[2.2]paracyclophan-4-yl. (i) K_2CO_3.

2.23. Carborane

To study the effects of carboranyl groups on the electronics (and ultimately on the polymerization) of [2.2]paracyclophane, Zakharkin and co-workers have prepared a series of carborane-bearing [2.2]paracyclophanes. Reaction of **46** with 1-lithio-*o*- and 1-lithio-*m*-carboranes (**268ab** and **272a**) furnished the corresponding paracyclophanyl carboranyl carbinols **266ab** and **271** (Scheme 63). Reaction of 1,2-dilithio-*o*- and -*m*-carboranes (**268c** and **272b**) with excess **46** gave the respective glycols **269a** and **269b**. Alkylation of 4-chloromethyl[2.2]paracyclophane (**270**) by **268a** provided **267**. The first hint of unusual behavior came when attempted Friedel–Crafts acylations of [2.2]paracyclophane by carboranecarbonyl chlorides gave only resinous products, although these chlorides are known to smoothly acylate benzenes. By contrast, *o*-carboraneacetyl chlorides **273ab** acylate [2.2]paracyclophane (**6**) to give ketones **274ab**. Reduction of **274b** under Clemmensen conditions

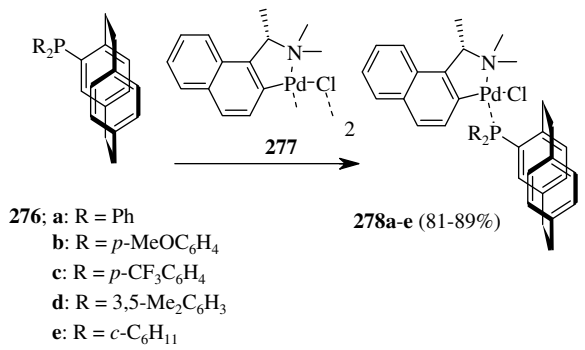
gave secondary alcohol **275**, a transformation also effected by $LiAlH_4$. In general, the authors found that 1-acylcarboranes and 1-phenacylcarboranes (either *o*- or *m*-) underwent abnormal Clemmensen reduction to the alcohols, as did 4-(phenylacetyl)[2.2]paracyclophane. By contrast, carboran-1-ylacetones were reduced normally to propylcarboranes, and 1-phenacylmethyl-*o*-carborane was reduced to 1-(γ-phenylpropyl)-*o*-carborane. The abnormal reductions were attributed to the carboranyl group lowering both the basicity and the reduction potential of the ketones.[105]



Scheme 63. Chemistry of carboranyl [2.2]paracyclophanes. (i) **273a** or **273b**, THF, 20 °C (**266a** 91%, **266b** 83%); (ii) **268c**, Et_2O, reflux (**269a** 89%); (iii) **272b**, Et_2O, reflux (**269b** 85%); (iv) **268a**, Et_2O/PhH, reflux (88%); (v) **272a**, THF, 20 °C (93%); (vi) $AlCl_3$, CH_2Cl_2, −10° to 20 °C (**274a** 80%, **274b** 85%); (vii) (**274b** to **275b**) Zn(Hg)/HCl (yields are not mentioned) or $LiAlH_4$ (88%).

2.24. Palladacycles

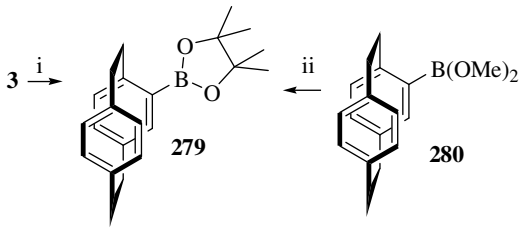
Hou has used palladacycles as chiral auxiliaries to resolve phosphino paracyclophanes. Reaction of racemic phosphines **276a–e** with the chiral palladacycle (*S*)-**277** gave the diastereomeric palladacycle-bearing paracyclophanes (R_p,*S*)- and (S_p,*S*)-**278a–e** (Scheme 64). After separation, treatment with sodium (*S*)-prolinate released the homochiral phosphines (R_p)- and (S_p)-**276a–e**.[106]



Scheme 64. Resolution of phosphino [2.2]paracyclophanes via palladacycles.

2.25. 2,1,3-Boradioxolane

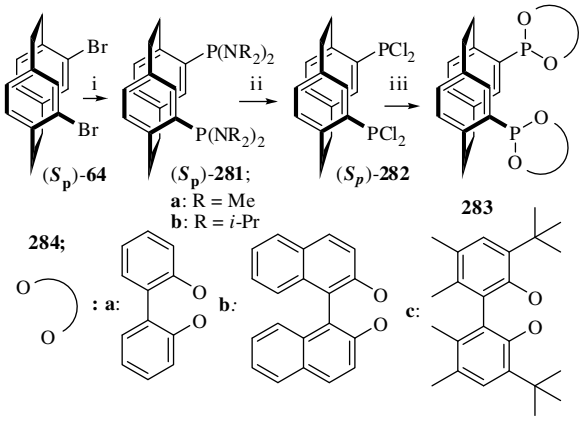
Exploring Suzuki couplings of [2.2]paracyclophane derivatives, Roche and Canturk reported that reaction of **3** with butyllithium followed by bis(pinacolato)diboron furnished 2-([2.2]paracyclophan-4-yl)-2,1,3-boradioxolane (**279**). The same product was obtained on transesterification of dimethyl [2.2]-paracyclophane-4-boronate (**280**) with pinacol (Scheme 65). Unlike **280**, the diisopropyl ester of the same boronic acid, or the boronic acid itself, **279** was stable in air and could be purified, but this stability made **279** very unreactive under Suzuki coupling conditions. Some reasonably efficient couplings were obtained by generating **280** in situ.[107]



Scheme 65. Preparation of 2-([2.2]paracyclophan-4-yl)-2,1,3-boradioxolane. (i) (1) BuLi, THF, −78 °C, (2) bis(pinacolato)-diboron, THF, −78 °C to rt (71%); (ii) pinacol (yields are not stated).

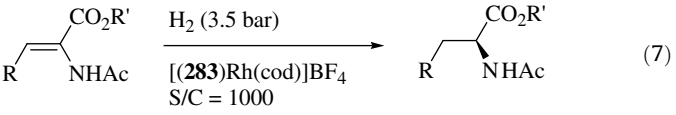
2.26. Cyclic phosphonite (1,3,2-dioxaphosphepane)

In 2001, a group at Chirotech prepared a series of cyclic phosphonites on a [2.2]paracyclophane framework, as ligands for asymmetric hydrogenation. Lithiation of (S_p)-4,12-dibromo[2.2]-paracyclophane [(S_p)-**64**], followed by reaction with a chlorobis(dialkylamino)phosphine, gave phosphinamides (S_p)-**281ab** (Scheme 66). Hydrogen chloride converted these into bis-(dichlorophosphine) (S_p)-**282**. This product was treated with the dilithium salts of 2,2′-biphenol (**284a**), (R_a)- or (S_a)-2,2′-binaphthol (**284b**), and (R_a)- or (S_a)-3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethylbiphenol (**284c**) to furnish the corresponding phosphonites **283**. The conformationally labile **284a** gave a single phosphonite, and diols **284b** and **284c** are resolvable, so five different phosphonites were made: (S_p)-**283a**, (S_p,R_a)- and (S_p,S_a)-**283b**, and (S_p,R_a)- and (S_p,S_a)-**283c**. The authors comment that stepwise synthesis via **281** and **282** was easy to implement, flexible, and led to pure **283**;[108] one suspects that phosphorus was most easily installed as a phosphinamide, while chloride is more nucleofugal than dialkylamide.



Scheme 66. Preparation of cyclic phosphonites on paracyclophane frame. (i) (1) *t*-BuLi, Et_2O, −78 °C, (2) $ClP(NR_2)_2$, rt (74–84%); (ii) HCl, Et_2O, rt (62–73%); (iii) dilithium salt of **284a–c**, THF, rt (48–72%).

The $[Rh(cod)]BF_4$ complexes of ligands **283** were studied as catalysts for the asymmetric hydrogenation of *N*-acetyldehydroamino acids and esters (Eq. 7). At a substrate/catalyst ratio of 1000, hydrogenation of methyl 2-acetamidoacrylate using ligand **283a** was quantitative in 0.5–3 h in protic or aprotic solvents, and gave (*S*)-product in 96–99% ee. The ligands showed a pronounced match/mismatch effect: (S_p,R_a)-**283b** gave essentially the same result as **283a**, but (S_p,S_a)-**283b** gave a catalyst much less active and selective. The bulky ligand (S_p,R_a)-**283c** furnished a catalyst still less active and selective than that from (S_p,S_a)-**283b**. All the catalysts gave (*S*) product predominantly, no matter what the identity or axial chirality of the phosphonite.[108]



(7)

3. Heterocycle fused to benzene ring

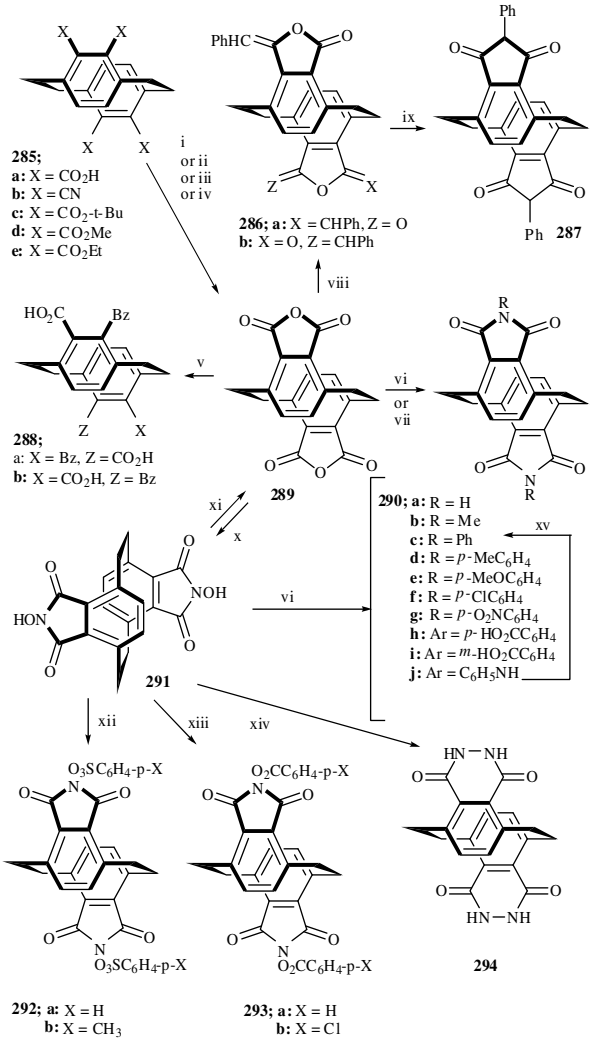
These structures raise questions of notation and organization. Strictly speaking, a [2.2]paracyclophane fused to a heterocycle is no longer a [2.2]paracyclophane, since at least one of its benzene rings has been formally replaced by a benzo-fused heterocycle.[109] If the fused heterocycle is non-symmetric, the ring system created by its fusion depends on the *position* of fusion: e.g. a [*b*]-fused pyridine creates a quinolinophane, while a [*c*]-fused pyridine creates an isoquinolinophane. For clarity, this chapter will be organized by fused heterocycle, and within each heterocycle by position of fusion.

3.1. Pyrrole, [*b*]-fused

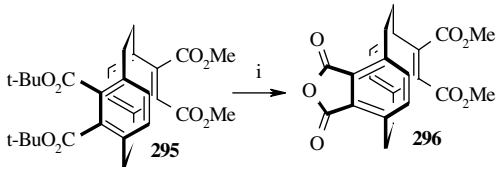
The known examples of this system[78,79] appear in Section 2.16, because most of them also bear pendant piperazines.

3.2. Pyrrole, [*c*]-fused; furan, [*c*]-fused; pyridazine, [*d*]-fused; 1,4-oxazocine, [*f*]-fused; 1,4-thiazocine, [*f*]-fused; isoindole, [*e*]-fused

In 1972 Hopf reported that [2.2]paracyclophane-4,5,12,13-tetracarboxylic acid (**285a**) upon attempted recrystallization from acetic acid gave the dianhydride **289** (Scheme 67).[110,111] The dianhydride could also be obtained from the tetranitrile **285b**[111] or the esters **285c**–**e** under a variety of acid-promoted or thermal conditions. In turn, **289** acylated benzene under Friedel–Crafts conditions to provide a mixture of **288ab**, and reacted with ammonia or primary amines to furnish imides **290a**–**c**.[112] Mourad, in 1983, described fusion of **289** with *N*-aryl-carbamates to furnish bis-imides **290c**–**g**; **290c** could also be prepared by refluxing **289** in aniline. Fusion of **289** with excess phenylacetic acid in the presence of sodium acetate afforded a mixture of the regioisomeric condensation products **286ab**; this mixture slowly rearranged to bis-dione **287** on exposure to sodium methoxide solution.[113] Eltamany and Mourad reported that the reaction of **289** with hydroxylamine hydrochloride furnished *N*,*N*′-dihydroxy-bisimide **291**, a transformation which could be reversed by aqueous base. This product in turn underwent sulfonation to **292ab** or acylation to **293ab**. Reaction of **291** with ammonia returned **290a**, anilines gave **290c**–**e** and **290g**–**h**, and hydrazine provided **294** (although phenylhydrazine gave **290j**). Thermolysis of **290j** led to loss of NH_3 and formation of **290c**, presumably via an *N*-phenyl analogue of **294**.[114] Heating of the mixed ester **295** led to loss of the *tert*-butyl esters with formation of an anhydride, but left the methyl esters intact, giving mono-anhydride **296** (Scheme 68).[115]



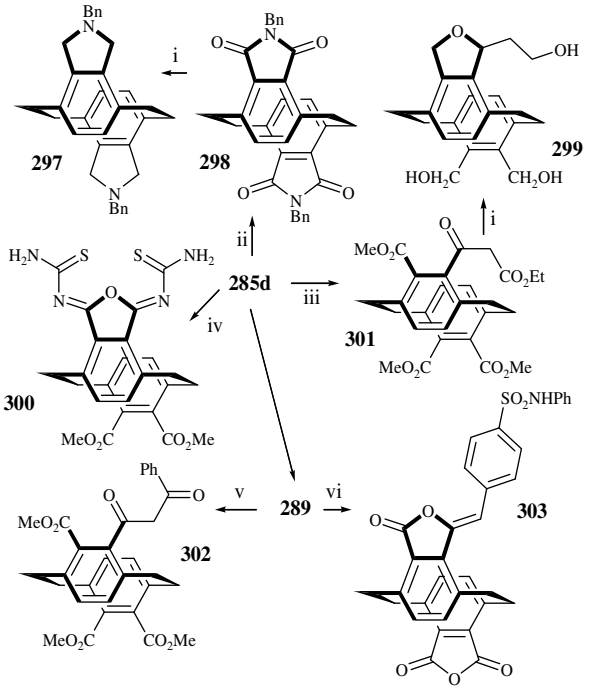
Scheme 67. Preparation and reactions of paracyclo-phanetetracarboxylic dianhydride. (i) **285a**+HOAc, heat (quant.); (ii) **285b**+concd HCl/HOAc (1:1), heat, 14 d (80%); (iii) **285c**–**e**, concd H_2SO_4 (quant.); (iv) **285c**, 230 °C, 2 h (quant.); (v) C_6H_6, $AlCl_3$; (vi) RNH_2 (**289** to **290a** 99%, **290b** 98%, **290c** 87%; **291** to **290a** 84%, **290c** 90%, **290d** 92%, **290e** 95%, **290h** 86%, **290i** 88%, **290j** 83%); (vii) $RNHCO_2Et$, 220 °C, 5 h (**290c** 89%, **290d** 91%, **290e** 94%, **290f** 89%, **290g** 92%); (viii) $BnCO_2H$, NaOAc, 240–250 °C, 6 h (67% of mixture); (ix) NaOMe, MeOH, reflux, 12 h (40%); (x) H_2NOH, pyridine, reflux, 1 h (89%); (xi) KOH, n-$C_5H_{11}OH/H_2O$, reflux (91%); (xii) p-X-$C_6H_4SO_3Cl$, pyridine, $CHCl_3$, rt (**292a** 94%, **292b** 91%); (xiii) p-X-$C_6H_4CO_2Cl$, pyridine, $CHCl_3$, rt (**293a** 91%, **293b** 92%); (xiv) $H_2NNH_2\cdot H_2O$, HOAc, reflux, 6 h (92%); (xv) 400–450 °C, 2 h (74%).



Scheme 68. Mono-anhydride from mixed ester. (i) 220 °C, 2.5 h (84%).

Aly et al. have elaborated **285d** and **289** to a variety of products (Scheme 69). Reaction of **285d** with benzylamine provided bis-imide **298**, which was reduced with $LiAlH_4$ to give diamine **297**.[116] Fusion of **285d** with excess thiourea led to **300**, which formally results from condensation of thiourea with **296**; whether **296** in fact intervenes is unknown. Claisen condensation of **285d** with ethyl acetate enolate gave **301**, the $LiAlH_4$ reduction of which provided oxolene **299**. Condensation of dianhydride **289** with acetophenone enolate led to opening of one anhydride to give **302**; fusion of **289** with *p*-(phenylsulfamoyl)-benzeneacetic acid led to

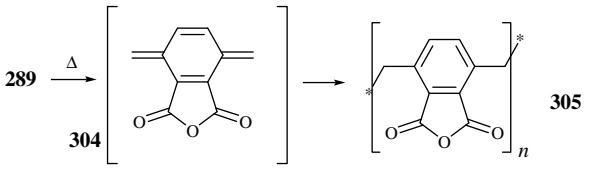
condensation product **303**. This last reaction, and that of **285d** with thiourea, involved partial reaction with excess reagent; the authors attributed these results to transannular electronic de-activation of the second benzene ring.[116]



Scheme 69. Elaboration of tetramethyl [2.2]paracyclo-phanetetracarboxylate and [2.2]paracyclophanetetracarboxylic bisanhydride. (i) $LiAlH_4$, THF (**287** 45%, **289** 40%); (ii) $BnNH_2$, 100 °C, 2 h (84%); (iii) EtOAc, Na (1 equiv; 60%); (iv) thiourea, 140 °C, 1 h (59%); (v) acetophenone, NaOMe (1 equiv) (64%); (vi) HO_2CCH_2-*p*-C_6H_4-($NHSO_2Ph$) (neat), 140 °C, 1 h (69%).

The groups of Gerson and Hopf generated radical anions of paracyclophanes including **289**, **290a–c**, and **286** either by electrochemical reduction in DMF, or by chemical reduction with potassium; these radical anions were characterized by ESR and ENDOR spectroscopy. Hyperfine couplings for paracyclophane radical anions were about half those observed for radical anions of analogously substituted benzenes (e.g., for **289** vs phthalic anhydride radical anion).[117]

Lahann and co-workers have extensively explored polymers derived from **289**. Pyrolysis of **289** at 620 °C and 0.2 mbar, followed by deposition onto stainless steel at 12 °C and the same pressure, furnished **305** as a thin film, presumably via polymerization of **304** (Scheme 70).[118]

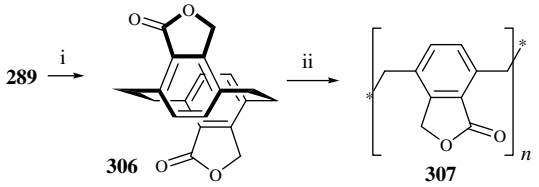


Scheme 70. Generation and polymerization of *p*-xylylene-2,3-dicarboxylic anhydride (yields are not stated).

An early application of **305** and other functionalized poly(*p*-xylylene)s was to coronary stents. Metallic stents are prone to re-stenosis, due to contact activation of cells of various types. Nickel-titanium coronary stents were coated with e.g. **305**; the functional groups of the coatings were used to immobilize the thrombin inhibitor, *r*-hirudin. The coated stents were found in vivo to be less thrombogenic than virgin metallic stents, and surface-bound *r*-hirudin decreased platelet aggregation drastically.[119]

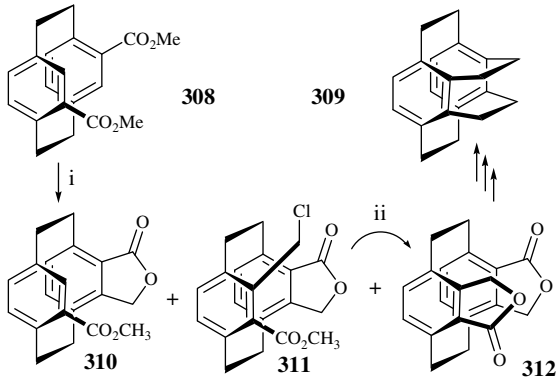
An advantage of **305** over other poly(*p*-xylylene)s is that, when attacked by biological nucleophiles, no toxic leaving group is released: the leaving group is the internal carboxylate. Therefore, **305** is of interest as a template for cell patterning. The polymer could be deposited, to a thickness of ca. 90 nm, on poly(TFE), polyethylene, silicon, gold, or glass, as well as stainless steel. The coating was patterned by microcontact printing of an amino-terminated biotin ligand; in turn, streptavidin selectively bound to the biotin-exposing surface regions, allowing localization of a biotin-tethered antibody against α_5-integrin, and thus spatially directed deposition of mammalian cells.[120]

Borohydride reduction of **289** furnished the bislactone **306**, which was polymerized to **307** (Scheme 71). In this study, fourteen different [2.2]paracyclophanes were thermolyzed to create poly(*p*-xylylene)s and study their optical properties. All formed transparent and topologically uniform films, of thicknesses varying from 50 to 781 nm. Anhydride **305** and lactone **307** were two of the thinner films, at 56 and 71 nm, respectively; of all the polymers studied, they showed the highest refractive indices and values of optical birefringence.[121,122]



Scheme 71. Generation and polymerization of *p*-xylylene 2,3-(γ-lactone). (i) $NaBH_4$ (72%); (ii) Δ.

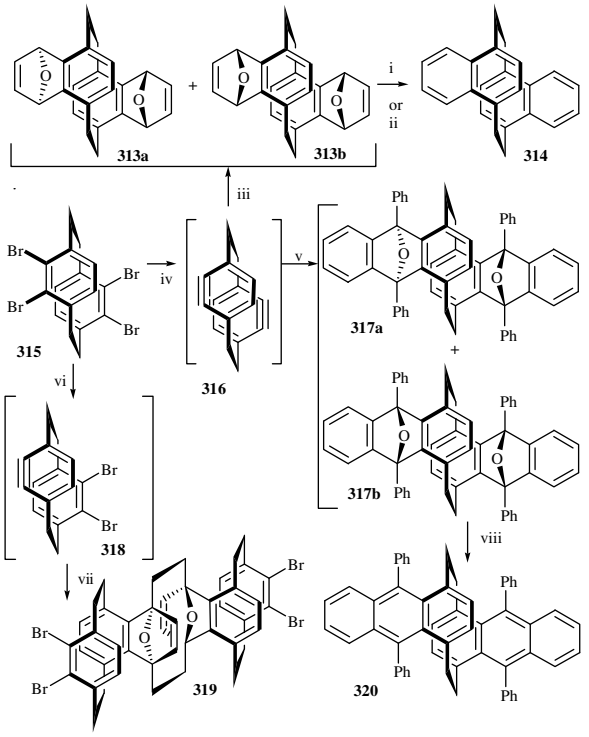
A different route to cyclophane-fused γ-lactones was demonstrated in 1979 by Kleinschroth and Hopf (Scheme 72). Reaction of dimethyl [2.2]paracyclophane-4,12-dicarboxylate (**308**) with CH_3OCH_2Cl and $AlCl_3$ gave **310–312**. Evidently, initial electrophilic chloromethylation is followed by ester cleavage and lactone closure. Saponification of isolated **311** gave **312**, which was then converted in three steps into [2.2.2.2](1,2,3,4)cyclophane (**309**).[123]



Scheme 72. [2.2.2.2](1,2,3,4)Cyclophane via cyclophane-fused γ-lactones. (i) MOMCl, $AlCl_3$ (**310** 32%, **311** 32%, **312** 9%); (ii) NaOH, MeOH/H_2O (86%).[123]

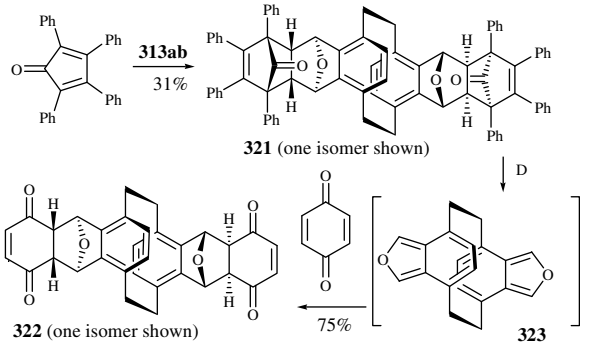
In 1969, Reich and Cram described the reaction of 4,5,12,13-tetrabromo[2.2]paracyclophane (**315**) with excess butyllithium in the presence of furan (Scheme 73), to furnish cycloadduct **313**, presumably via 4,12-[2.2]paracyclophadiyne (**316**); the stereochemistry of **313** was then unknown. Catalytic hydrogenation of **313** gave its tetrahydro derivative, which was heated with alcoholic acid to provide *anti*-[2.2](1,4)-naphthalenophane (**314**).[124] In 1993, de Meijere and co-workers showed **313** to be a mixture of *syn*,*syn* and *anti*,*syn* cycloadducts (**313a** and **313b**, isolated in 12 and 15% yields, respectively). Reductive deoxygenation of **313** (either

isomer) with low-valent titanium again afforded **314**. Similarly, trapping of **316** with diphenylisobenzofuran gave adducts **317a** and **317b**; these resisted deoxygenation with low-valent titanium, but could be deoxygenated with trimethylsilyl iodide to provide **320**. Treatment of **315** with *one* equivalent of butyllithium generated paracyclophyne **318**; **318** could be trapped with [2.2](2,5)furanophane to furnish the stair-like 2:1 adduct **319**, the internal oxygens of which resisted all attempts to remove them reductively.[125]



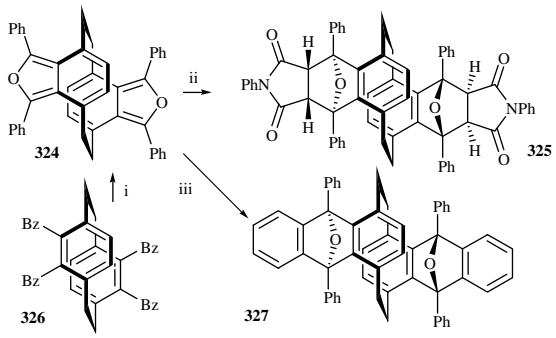
Scheme 73. Generation of paracyclophynes, and their cycloaddition with furans. (i) $TiCl_4$, $LiAlH_4$, NEt_3; (ii) (1) H_2, Adams's catalyst, (2) EtOH, HCl; (iii) furan (42–84%); (iv) *n*-BuLi (2 equiv); (v) diphenylisobenzofuran (**317a** 33%, **317b** 25%); (vi) *n*-BuLi (1 equiv); (vii) [2.2](2,5)furanophane; (viii) (from mixture of **317ab**) Me_3SiI.

When the mixture of **313ab**, generated as just described, was heated in benzene with excess tetraphenylcyclopentadienone, a mixture of stereoisomeric cycloadducts **321** was obtained in 31% yield (Scheme 74). In turn, heating of **321** in *o*-dichlorobenzene at 180 °C released the unstable parent [2.2](4,7)isobenzofuranophane (**323**), which was trapped in situ with benzoquinone to provide a stereoisomeric mixture of adducts **322**.[126]



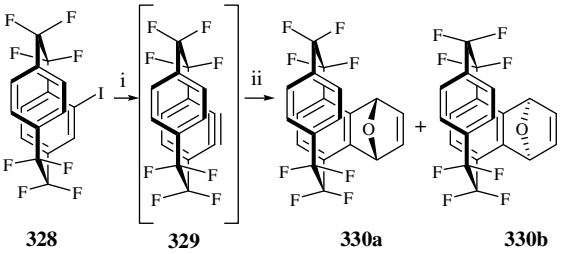
Scheme 74. Generation and trapping of [2.2](4,7)isobenzo-furanophane.

To generate a more stable analogue of **323**, 4,5,12,13-tetrabenzoyl[2.2]paracyclophane (**326**) was reduced to the corresponding tetraol and cyclized with acetic anhydride to furnish **324**; **324** indeed was stable, but underwent Diels–Alder reactions with *N*-phenyl-maleimide and benzyne to create adducts **325** and **327**, respectively, as mixtures of *syn*,*syn* and *syn*,*anti* stereoisomers (Scheme 75).[126]



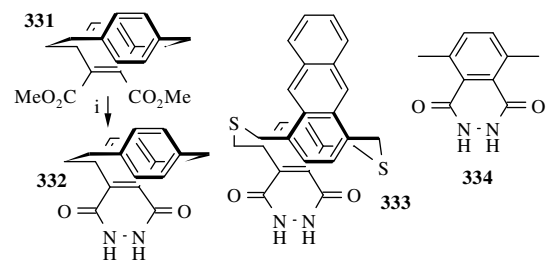
Scheme 75. Chemistry of tetraphenyl[2.2](4,7)isobenzofurano-phane. (i) (1) $LiAlH_4$, (2) Ac_2O (50%); (ii) *N*-phenylmaleimide, toluene, reflux (61% as mixture); (iii) *o*-$C_6H_4Br_2$, *n*-BuLi, THF, −40 °C to rt (*syn*,*anti*-**327** 24%, *syn*,*syn*-**327** 10%).

In 2003, Battiste, Dolbier, and co-workers generated octafluoro-4-[2.2]paracyclophyne (**329**) by dehydro-iodination of **328** with potassium *tert*-butoxide, and trapped **329** with a series of dienes of which furan was the lone heterocycle (the others were benzene, naphthalene, anthracene, [2.2]paracyclophane, and *tert*-butylbenzene). Trapping of **329** by furan gave a 5:3 *endo*/*exo* mixture of adducts **330ab** (Scheme 76). The isomers were distinguishable by ^{19}F NMR, and the structure of the *endo* adduct **330a** was confirmed crystallographically.[127]



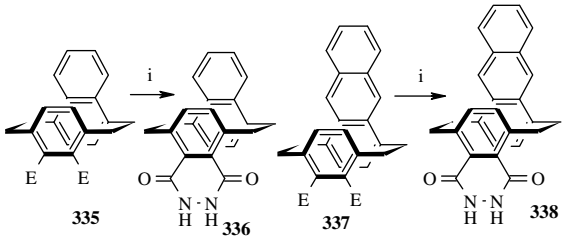
Scheme 76. Generation and trapping of octafluoroparacyclophyne. (i) *t*-BuOK; (ii) furan (80%; **330a**/**330b**=5:3).

The dihydropyridazinedione ring (phthalhydrazide) studied by Eltamany and Mourad (Scheme 67) had attracted attention earlier, because it can undergo oxidation, and then transfer electronic excitation energy to a luminophore, creating chemiluminescence. In 1973, Gundermann and Röker reported that hydrazinolysis of dimethyl [2.2]paracyclophane-4,5-dicarboxylate (**331**) gave phthalhydrazide **332** (Scheme 77). The fluorescence of **332** in DMSO/*t*-BuOK/O_2 (λ_{max}=395 nm) was considerably weaker than that of analogue **333**, the anthracene group of which is a better energy acceptor than the *p*-xylylene substructure of **332**, but **332** fluoresced more strongly than the model compound **334** by an order of magnitude.[128]



Scheme 77. Hydrazide from [2.2]paracyclophane-4,5-dicarboxylic acid, and models. (i) H_2NNH_2 (anhyd), 140 °C (autoclave; 60%).

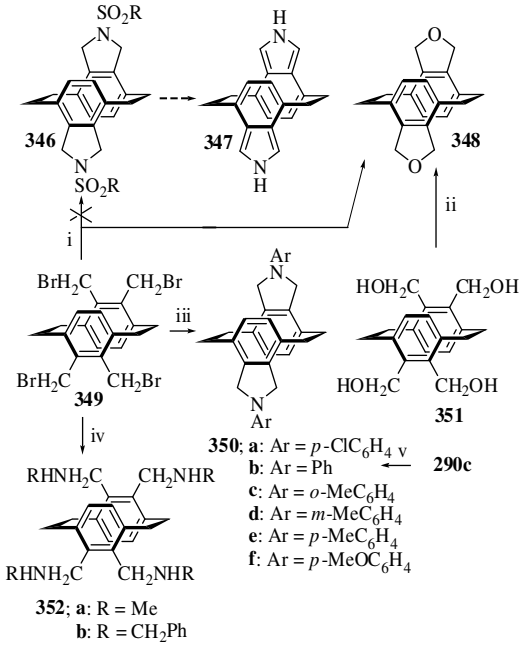
Phthalhydrazides incorporating naphthalene and anthracene acceptor groups, viz. **336** and **338**, were prepared by hydrazinolysis of diesters **335** and **337** (Scheme 78; note that **337** and **333** have a common precursor). Hydrazides **332**, **336**, and **338** all showed chemiluminescence either in an aprotic medium (e.g., DMSO/*t*-BuOK/O_2) or in an aqueous system (e.g., aq NaOH/hemin/H_2O_2). In the latter, **338** also showed weaker chemiluminescence than luminol, but only by 5-fold; in the aprotic medium, the chemiluminescence of **338** had a quantum yield 2.5-fold greater than that of **336**, and equal to that of luminol.[129]



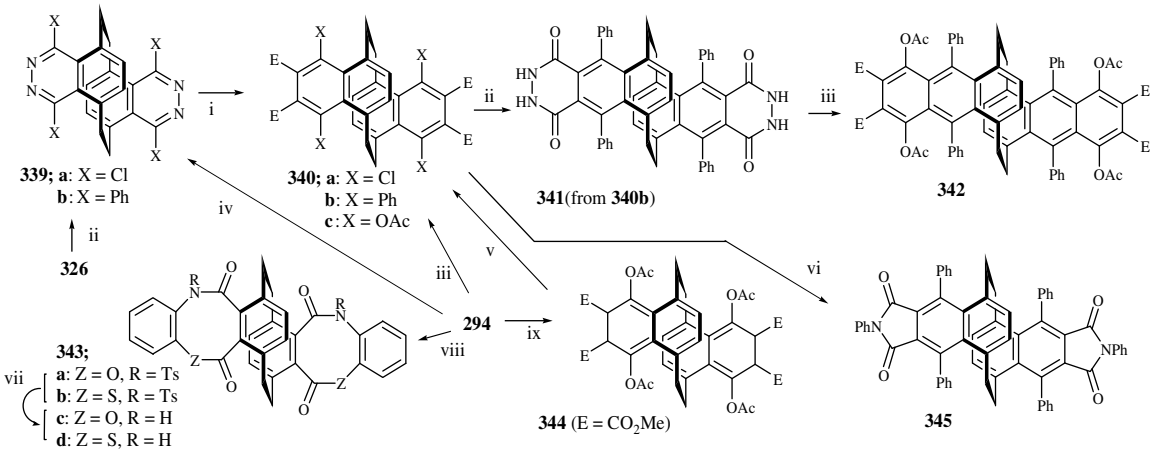
Scheme 78. Phthalhydrazides bearing naphthalene and anthracene acceptors. (i) H_2NNH_2 (anhyd), 140 °C (autoclave; **336** 71%, **338** 31%).

In 2003, Aly reported that the reaction of the bis(phthalhydrazide) **294** with PCl_5 gave the symmetric tetrachlorophthalazinophane **339a**, which in turn reacted with DMAD to provide tetrachloronaphthalenophane **340a**, presumably via double Diels–Alder reaction followed by extrusion of dinitrogen (Scheme 79). Reaction of **294** itself with DMAD and acetic anhydride afforded naphthalenophane **340c**; the rationale is that each ring is converted into the corresponding bis(acetoxy)phthalazine, followed again by Diels–Alder cycloaddition and loss of N_2. Consistent with this thinking, **294** and dimethyl maleate gave **344**, a tetrahydro analogue of **340c**; DDQ oxidation then converted **344** into **340c**. Reaction of tetrabenzoyl-paracyclophane **326** with hydrazine furnished tetraphenylphthalazinophane **339b** and thence **340b**. Tetraester **340b** reacted with aniline to give benzo[*f*]isoindolophane **345** and with hydrazine to give benzo[*g*]phthalazinophane **341**; reaction of **341** with DMAD and acetic anhydride gave anthracenophane **342**. Reaction of **294** with 2-(*N*-tosylamino)-phenol or 2-(*N*-tosylamino)-thiophenol in the presence of triethylamine leads to the only known members of two more heterocyclic classes: the oxazocine- and thiazocine-fused cyclophanes **343a** and **343b**, respectively. The appearance of the bridge protons as two different ^{1}H NMR four-spin systems establishes the regiochemistry as head-to-head (shown) not head-to-tail (exchange NR and Z on one half-structure). Acidic hydrolysis of the tosyl groups provides **343c** and **343d**.[130]

The parent [2.2](4,7)isoindolophane (**347**) remains unknown, although approaches to it were described in 1986 by Mourad. Reaction of tetrakis(bromomethyl)-paracyclophane (**349**) with anilines resulted in cyclizative alkylation to produce isoindolinophanes **350a–f** in 57–71% yields (Scheme 80). Compound **350b** could also be obtained by $LiAlH_4$ reduction of the corresponding bis-imide **290c**. Reaction of **349** with aliphatic amines led to 4-fold alkylation without cyclization, to give products **352ab**. It was hoped that reaction of **349** with sulfonamides might lead to *N*-sulfonylisoindolinophanes **346**, from which **347** might be obtained by elimination. However, reaction of **349** with either methane- or *p*-toluene-sulfonamide furnished **348** in 38–43% yields. The same product was obtained from acid-catalyzed dehydration of tetrakis(hydroxymethyl)paracyclophane (**351**).[131]



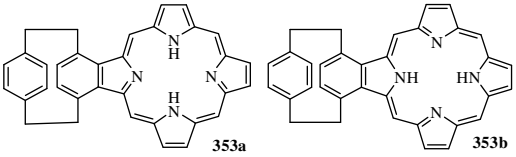
Scheme 80. Approach to [2.2](4,7)isoindolophane. (i) RSO_2NH_2, DMF, reflux (**348** 43% for R=Tol, 38% for R=Me); (ii) TsOH, $ClCH_2CH_2Cl$, 40–50 °C, 3 h (34%); (iii) $ArNH_2$, DMF, reflux (**350a** 71%, **350b** 68%, **350c** 69%, **350d** 57%, **350e** 60%, **350f** 64%); (iv) RNH_2, reflux, 6 h (**352a** 44%, **352b** 40%); (v) (to **350b**) $LiAlH_4$ (48%).



Scheme 79. Preparation and elaboration of phthalazinophanes. (i) DMAD, toluene, reflux (**340a** 80%, **340b** 92%); (ii) H_2NNH_2, DMF, 80 °C (**339b** 80%, **341** 80%); (iii) DMAD, AcOH, Ac_2O, reflux (**340c** 90%, **342** 95%); (iv) (to **339a**) PCl_5, DMF, 100 °C (90%); (v) DDQ; (vi) (from **340b**) $PhNH_2$, Et_2O, reflux (92%); (vii) H_2SO_4 (aq) (**343c** 85%, **343d** 80%); (viii) TsNH-*o*-C_6H_4-ZH, EtOH, Et_3N, reflux (**343a** 75%, **343b** 77%); (ix) dimethyl maleate.

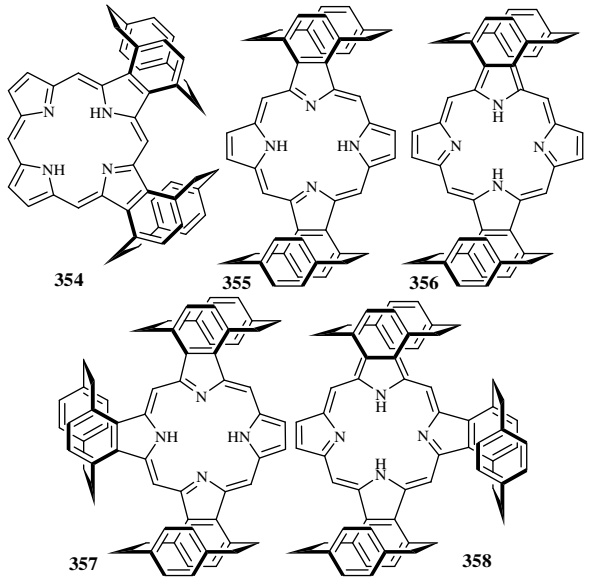
3.3. Porphine

Türker has carried out extensive semiempirical calculations on [2.2]cyclophanes fused to porphyrins (the parent system of phthalocyanines). First, heats of formation were calculated (AM1 method) for porphyrins fused to benzene, [2.2]orthocyclophane, [2.2]metacyclophane, and [2.2]paracyclophane. Each fusion is studied in position A or B: the paracyclophane-fused compounds are **353a** and **353b**, respectively (Scheme 81). For each fusion site, there are two regioisomeric orthocyclophanes; each *ortho*- or metacyclophane can exist as *syn* (folded) or *anti* (extended) conformers. For each fusion site, the paracyclophane was calculated to be the least stable isomer, **353a** being 5 kJ/mol less stable than **353b**. HOMO–LUMO gaps were predicted to be $\sim 0.04\times10^{-18}$ J less for all A isomers than for any B isomer; **353a** was calculated to have the lowest gap of all (0.9291×10^{-18} J), while **353b** had the highest (0.9760×10^{-18} J).[132]



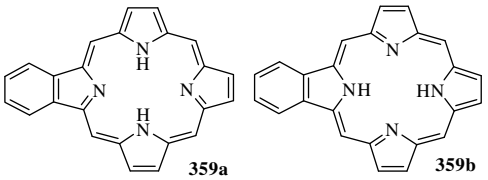
Scheme 81. Paracyclophanes fused to porphyrins.

The same treatment was applied to porphyrins fused to two or three [2.2]paracyclophane substructures. Three di-fused compounds **354**–**356** and two tri-fused compounds **357** and **358** are possible (Scheme 82; planar chiralities shown are random). HOMO–LUMO gaps are calculated to be lower (exception: **354**) for the parent, benzo-, or singly cyclophane-fused compounds; the lowest value for a di-fused structure is 0.84×10^{-18} J for **356**, and the lowest value of all is 0.81×10^{-18} J for **357**.[133]



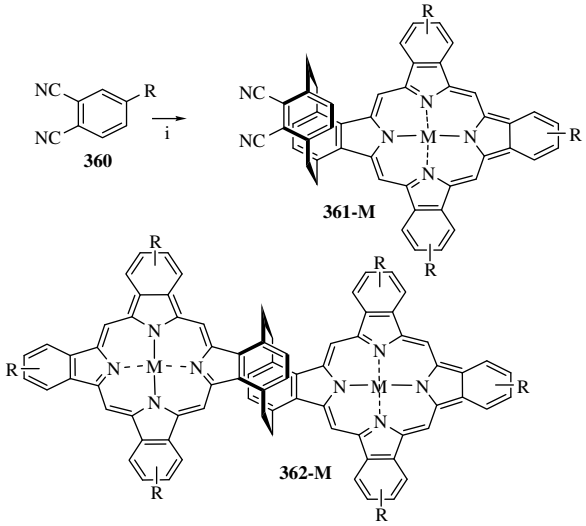
Scheme 82. Doubly and triply paracyclophane-fused porphyrins.

The Be^{II}, Si^{II}, Si^{IV}, Ge^{II}, Ge^{IV}, and Zn^{II} complexes of **353** were treated; with metal bound, the distinction between **353a** and **353b** disappears. Complexes of the tetravalent ions were predicted to be more stable than those of the dications; of the dications, the rare ion Si^{II} was calculated to give the most stable complex, and Zn^{II} the least. The same stability order was predicted for complexes of singly benzo-fused porphyrins (**359**: Scheme 83). For complexes of **353**, the greatest HOMO/LUMO gap was predicted for the Si^{II} complex (0.99×10^{-18} J), and the smallest for the Ge^{II} complex (0.81×10^{-18} J).[134] To predict optical spectra, ZINDO/S calculations were carried out on **353ab** and **359ab.** Longest-wavelength transitions are predicted in the wavelength order: **353a**>**359a**>**353b**>**359b**.[135]



Scheme 83. Singly benzo-fused porphyrins.

In 2007, Kobayashi and co-workers condensed 4,5,12,13-tetracyano[2.2]paracyclophane (**285b**) with 4-*tert*-butyl-phthalonitrile (**360**) in the presence of Zn^{II} to afford a mixture of **361**–Zn and the [2.2](1,4)phthalocyaninophane complex **362**–Zn (Scheme 84). Reaction of **285b** with **360** in the presence of CuCl gave **361**–Cu, which was treated with $CuCl_2$ and additional **360** to provide a small amount of **362**–Cu (the *tert*-butyl groups are distributed between poisitions 3 and 4 on each benzo ring). The cyclophane frameworks of complexes **362** define a slipped-stack arrangement of the phthalocyanine units, similar to those of bacteriochlorophyll subunits in photosynthetic light-harvesting antennae. In the absorption spectra, the 678-nm absorption band of tetrabutylated zinc phthalocyanine was split into well-resolved bands at 683 and 706 nm in **361**–Zn, but **363**–Zn showed much greater splitting and red-shifting, to 690 and 753 nm. Together with data from magnetic circular dichroism and fluorescence spectra, it was concluded that significant π–π interactions are involved in the excited singlet states of **362**–Zn. The copper complexes behaved almost identically.[136]

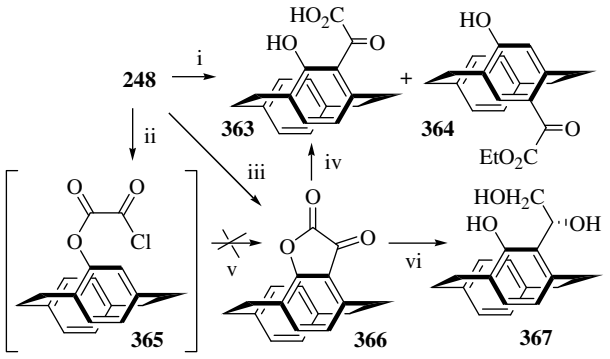


Scheme 84. Phthalocyaninophanes. (i) **285b**, metal ion. R=*t*-Bu: **361**-Zn 7.4%, **362**-Zn, 2.1%, **361**-Cu 18%, **362**-Cu 0.7% from **361**-Cu.

3.4. Furan, [*b*]-fused; pyran, [*b*]-fused

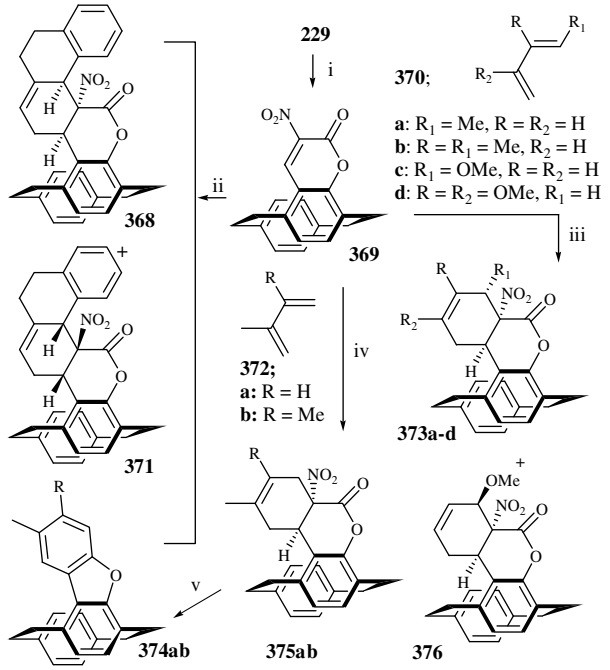
Three [2.2]paracyclophanes bearing [*b*]-fused furans are shown in Section 2.16 above.[80] Rozenberg and Hopf find that oxaloylation of [2.2]paracyclophan-4-ol (**248**) depends strongly on the conditions. Reaction of **248** and oxalyl chloride in the presence of $AlCl_3$ gave partial conversion into a mixture of *o*- and *p*-acylated products

(**363** and **364**, respectively), but use of $TiCl_4$ as catalyst resulted in rapid near-quantitative *o*-acylation and cyclization, to give furandione-fused cyclophane **366** (Scheme 85).[89] This product was stable to aqueous or alcoholic acid or base, but suffered ring opening to **363** on silica gel.[89] Product **366** could *not* be obtained via O-acylation of **248**, the product of which (formed under nucleophilic catalysis by DMAP, and presumed to be **365**) would not cyclize.[89] Crystal structures were obtained for both racemic and resolved **366**;[89,137] $LiAlH_4$ reduction of **366** results in hydride attack on the ketone from the less-hindered face of the cyclophane, followed by reductive cleavage of the lactone, to give **367**.[89]



Scheme 85. Formation and reactions of furandione-fused [2.2]paracyclophane. (i) (1) $(COCl)_2$, $AlCl_3$, CH_2Cl_2, (2) EtOH; (ii) $(COCl)_2$, DMAP (**363** 16%, **364** 6.5%); (iii) $(COCl)_2$, $TiCl_4$, CH_2Cl_2 (96–99%); (iv) SiO_2, $CHCl_3$ (81%); (v) $AlCl_3$ or $TiCl_4$; (vi) $LiAlH_4$, Et_2O, reflux; 94:6 dr (**367** isol. 58%).

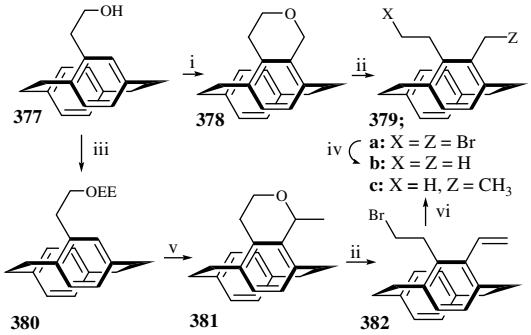
In 2005, Minuti reported that condensation of 5-hydroxy-[2.2]paracyclophane-4-carbaldehyde (**229**) with ethyl nitroacetate afforded α-pyrone-fused paracyclophane **369** (Scheme 86). Diels–Alder reactions of **369** proceeded at 1 atm only slowly with **372a**, and not at all with **372b**, but at 8 kbar pressure, they gave adducts **375ab** in 80–98% yields.[138] Elimination of HNO_2 from **375ab** using DBN, followed by DDQ oxidation, produced benzofurans **374ab**. Transformation of **375ab** into **374ab** could also be accomplished by hydrolysis/decarboxylation with aqueous NaOH, followed by in situ Nef cyclodehydration with sulfuric acid.[139] Pentadiene (**370a**) and **369** would react only at 8 kbar, to give adduct **373a** in 53% yield. The reaction between **369** and 2-methyl-1,3-pentadiene (**370b**) afforded **373b** in 33% yield at atmospheric pressure, but in 64% yield at 8 kbar. Cycloadditions with **370a** and **370b** all proceeded with exclusive *anti-exo* stereoselectivity. *anti* Selectivity versus the paracyclophane unit is unsurprising, given the severe steric hindrance imposed by the phane structure, but the unusual *exo* selection was attributed to a secondary-orbital interaction between the diene and the nitro group. Reactions of **369** with **370c** and **370d** gave the respective adducts at atmospheric pressure in 42 and 67% yields, respectively, but in higher yields at 8 kbar (69 and 98%). The exclusive adduct from **370d** was the *anti-exo* adduct **373d**, but **370c** under both sets of cycloaddition conditions gave ~2:1 mixtures of **373c** (minor) and *anti-endo* adduct **376**. Reaction of **369** with 1,2-dihydro-3-vinylnaphthalene gave cycloadducts in 70–75% yields at either atmospheric pressure or 8 kbar; all adducts obtained were *endo*, but at 8 kbar there was an 18:1 preference for the anti isomer **368** over the *syn* adduct **371**, while at normal pressure the preference was only 2:1.[138]



Scheme 86. Pyrone- and benzofuran-fused [2.2]paracyclophanes. (i) $O_2NCH_2CO_2Et$, piperidine/HOAc, *n*-BuOH, 110 °C (72%); (ii) **369** (70–75%; **368**/**371**=18:1 at 8 kbar, 2:1 at 1 bar); (iii) see text for conditions and yields; (iv) 8 kbar, CH_2Cl_2, 65 °C (**375a** 80%, **375b** 98%); (v) (1) DBN, THF, rt, 22 h, (2) DDQ, PhH, reflux (**374a** 20%, **374b** 28%) or (1) 3 M NaOH, (2) 3.75 M H_2SO_4 (**374a** 32%, **374b** 30%).

3.5. Pyran, [*c*]-fused

In 1989, Psiorz and Schmid reported the syntheses of 4,5-diethyl- and 4-ethyl-5-methyl[2.2]-paracyclophanes (**379c** and **379b** respectively), both of which proceeded via pyrans (Scheme 87). The common starting material was 4-(β-hydroxy-ethyl)[2.2]-paracyclophane (**377**), which gave pyran **378** on reaction with paraformaldehyde in CH_2Cl_2 containing HCl gas; ring opening with BBr_3 furnished dibromide **379a**, reductive debromination of which ($LiAlH_4$) provided **379b**. Conversion of **377** into its α-ethoxyethyl ether **380**, followed by cyclization promoted by $TiCl_4$, gave pyran **381**. Ring opening (BBr_3) to **382**, followed by reduction (H_2/Pd then $LiAlH_4$), afforded **379c**.[140]



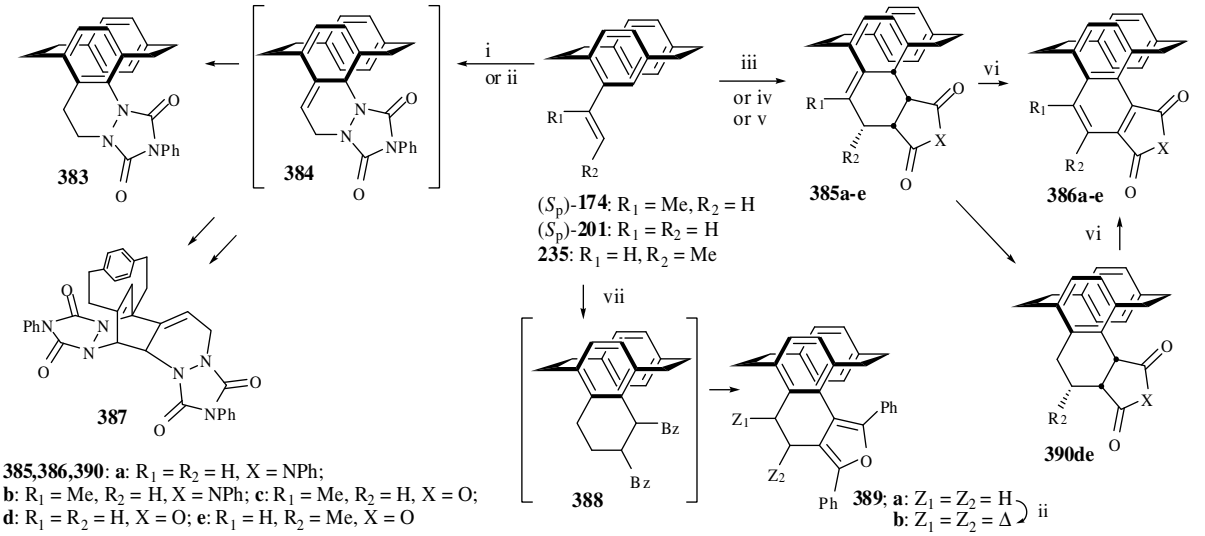
Scheme 87. *ortho*-Dialkylparacyclophanes via pyrans. (i) Paraformaldehyde, HCl(g), CH_2Cl_2, reflux (79%); (ii) BBr_3, CH_2Cl_2, (**379a** 96%, **382** 66%); (iii) EtOCH=CH_2, cat. concd HCl, CH_2Cl_2, rt (100%); (iv) $LiAlH_4$, THF, 50 °C (89%); (v) $TiCl_4$, CH_2Cl_2, rt (66%); (vi) (1) H_2/Pd, 3 bar, EtOAc, 50 °C, (2) $LiAlH_4$, THF, 45 °C (50%).

3.6. Indolizine, [*b*]-fused

The only two examples of this system, compounds **185ab**, are described above (Section 2.15): they are formed from systems with pendant pyridine rings, in reactions that form other such systems.[67]

3.7. Isoindole and isobenzofuran, [*d*]-fused

In 2001, the Perugia group reported that reaction of (S_p)-4-vinyl[2.2]paracyclophane (**201**) with *N*-phenylmaleimide takes

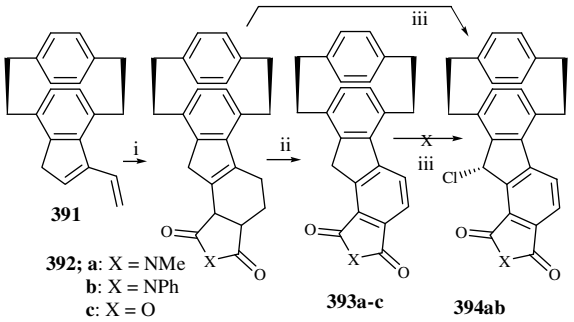


Scheme 88. 4-Alkenyl[2.2]paracyclophanes as Diels–Alder dienes. (i) **201**+NPTD, acetic acid, reflux, 5 d (**383** 64%); (ii) **201**+NPTD, toluene, cat. CF_3CO_2H, rt, 7 d (**387** 65%); (iii) *N*-phenylmaleimide, CH_2Cl_2, (**385a** 10 kbar, 40 °C, 70%; **385b** 7 kbar, rt, 80%); (iv) maleic anhydride, 7 kbar, CH_2Cl_2, 50 °C (**385c** 67%); (v) maleic anhydride, AcOH, 120 °C, 5 d (**390d** 72%, **390e** 54%); (vi) DDQ (**389b** 93%, **386a** 84%, **386b** 78%, **386c** 55%; **386d** from **390d** 67%, **386e** from **390e** 65%); (vii) **206**+BzHC=CHBz, AcOH, Ac_2O (**389a** 91%).

place only at high pressure and provides adduct **385a** (Scheme 88); in refluxing toluene at atmospheric pressure, there was no reaction. Compound **201** also acts as a Diels–Alder diene toward benzoquinone and 3-nitrocyclohexen-2-one,[141] although it undergoes other reactions with quinoline-5,8-dione and isoquinoline-5,8-dione (Scheme 48 above).[75] It was also found that 4-isopropenyl-[2.2]paracyclophane (**174**) reacts with *N*-phenylmaleimide and maleic anhydride only at high pressure (here, 7 kbar);[142,143] DDQ oxidation of adducts **385a–c** furnishes **386a–c**.[141–143] NMR studies and semiempirical calculations on **386bc** have been described.[144] In 2006, Aly, Hopf, and co-workers reported that reaction of **201** with maleic anhydride in acetic acid (reflux, 5 d) gave adduct **390d**, presumably via isomerization of the first-formed **385d**. Reaction of 4-[(*E*)-1-propenyl][2.2]paracyclophane (**235**) with maleic anhydride similarly gave **390e**, presumably via **385e**. Vinyl[2.2]paracyclophane (**201**) also acts as a Diels–Alder diene towards 1,2-dibenzoylethene in AcOH/Ac_2O; the furan **389a** presumably forms by in situ cyclization of adduct **388**. DDQ oxidation of **389a** and **390de** gives **389b** and **386de** respectively. Most spectacularly, equimolar amounts of **201** and *N*-phenyl-triazolinedione (NPTD) react in toluene containing catalytic CF_3CO_2H (rt, 7 d) to give the bisurazole **387**, the formation of which is attributed to two Diels–Alder cycloadditions followed by an acid-catalyzed Wagner–Meerwein shift.[83] The aromatized isomer **383** of the first-formed adduct **384** was previously isolated by Aly and Mourad, from reaction of **201** with 1 equiv NPTD in acetic acid at reflux for 5 d.[145]

3.8. Remotely fused pyrroles and furans

In 2004, the Perugia group reported that reaction of the vinyl-substituted indenoparacyclophane **391** with *N*-methylmaleimide, *N*-phenyl-maleimide, or maleic anhydride at 8.5 kbar gave the corresponding Diels–Alder adducts **392a–c** (Scheme 89). Treatment of toluene solutions of **392a–c** with 10% Pd/C at reflux for 48 h gave the aromatized phanes **393a–c** in 45–58% yields.[146] Reaction of **392a** or **392b** with DDQ gave the aromatized, chlorinated products **394ab**; these were *not* formed on treatment of **393ab** with DDQ, so that DDQ must have reacted with **392ab** as both oxidant and chlorine source.[147]



Scheme 89. Vinyl-substituted indenoparacyclophane as Diels–Alder diene. (i) *N*-Methylmaleimide, *N*-phenylmaleimide, or maleic anhydride (CH_2Cl_2, 8.5 kbar, rt; **392a** 72%, **392b** 75%, **392c** 52%); (ii) 10% Pd/C, toluene, reflux, 48 h (**393a** 57%, **393b** 58%, **393c** 45%); (iii) DDQ, toluene, reflux (**394a** from **392a** 30%, **394b** from **392b** 51%).

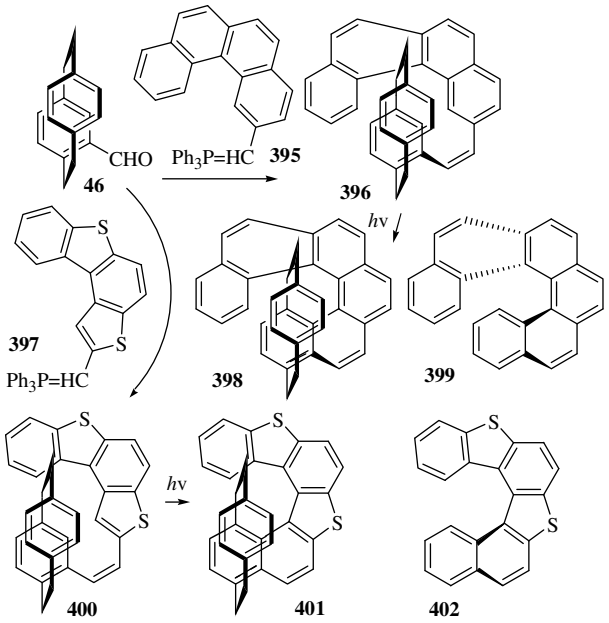
3.9. Remotely fused thiophenes and quinoxalines

Hexahelicene **398** was prepared from **46** by Wittig reaction with ylide **395**, followed by iodine-promoted oxidative photocyclization of alkene **396** (Scheme 90).[148] An analogous synthesis of heterohelicene **401** from **46** via **397** and **400** was also outlined.[148,149] UV and ORD spectra of **398**, **401**, the parent (−)-hexahelicene **399**, and heterohexahelicene **402** show the same chirality, which had been demonstrated crystallographically for **402**.[148]

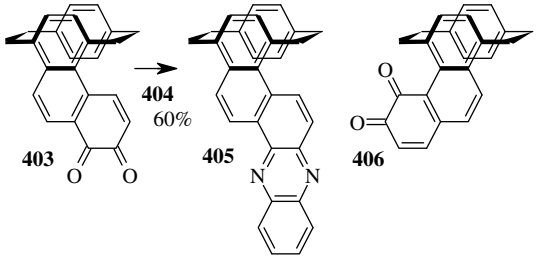
As mentioned above (Section 2.9), lower thiahelicenophanes were described in 2007 by Hopf.[34] The same paper reported reactions of paracyclophenanthroquinonophanes **403** and **406** with *o*-phenylenediamine (**404**). Quinone **403** condensed with **404** to furnish quinoxalino[2,3-*i*][2.2](1,4)phenanthrenoparacyclophane (**405**) in 60% yield, but **406** would not condense with **404**, presumably because of hindrance between the incipient quinoxaline ring and the paracyclophane subunit (Scheme 91).[34]

3.10. Oxazol-2(3*H*)-one, [*c*]-fused

Resolved (R_p)-4-hydroxy[2.2]paracyclophane (**248**) can be converted in a few steps into (R_p)-4-OMOM-5-amino[2.2]paracyclophane (**407**). In 2000, the Perugia group reported that hydrolysis of the MOM ether and reaction with ethyl chloroformate furnished oxazolone **408**, a planar-chiral auxiliary for synthesis of

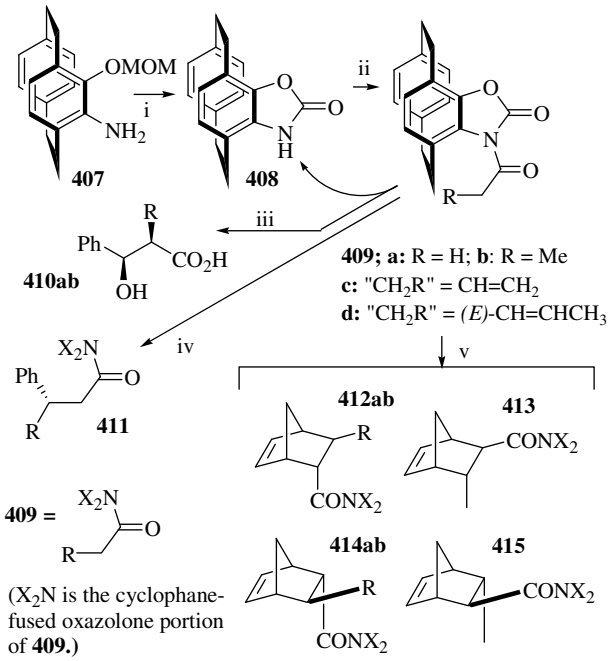


Scheme 90. Synthesis of chiral heterohexahelicene. Yields not stated.



Scheme 91. Reactions of phane-derived quinones with phenylenediamine.

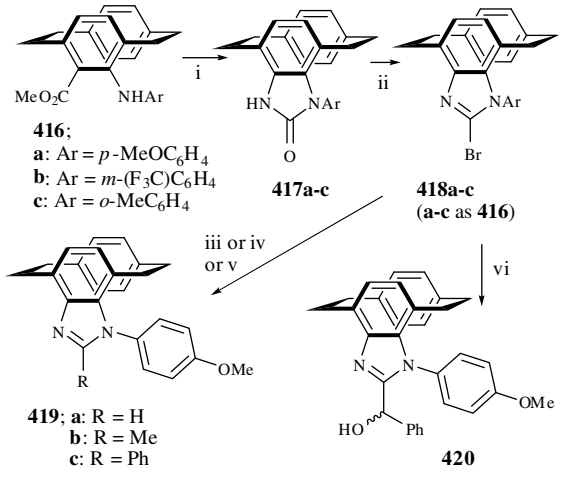
β-hydroxy acids. Deprotonation of **408** with BuLi, followed by N-acylation with an acyl chloride, provided **409ab**. Generation of a boron enolate (Bu_2OTf/Et_3N), aldol condensation with benzaldehyde, and oxidative workup (H_2O_2) gave β-hydroxy acids **410ab** in 71–90% ee. Predominant absolute configuration at the hydroxyl-bearing carbon was (*R*) from the (R_p) auxiliary; that is, reaction occurred preferentially between the *si*-face of the acyloxazolone and the *re*-face of benzaldehyde. In **410b**, the *syn*/*anti* ratio was 80:20 (Scheme 92); auxiliary **408** was recovered.[150,151] Acylation of **408** with α,β-enoyl chlorides furnished *N*-acyloxazoles **407cd**, which underwent Diels–Alder reactions with cyclopentadiene. In the presence of Et_2AlCl in CH_2Cl_2 at −78 to −100 °C, the reactions proceeded in 5–10 min. Dienophile **409c** gave (70%) an 86:14 mixture of *endo* adducts **412a** and **414a**, and **409d** gave (90%) a 96:2:2 mixture of **412b**, **414b**, and **413;** that is, *endo* selectivity was almost complete, and attack was predominantly from the less hindered *re*-face of the *s-cis* bidentate Et_2Al complex of the dienophile, in which the carbonyl groups are aligned parallel as shown. Without Et_2AlCl, in either CH_2Cl_2 or water, reaction of **409d** with cyclopentadiene was much slower (40–42% conversion after 30 h at rt). In water, an 89:8:2 mixture of **414b**, **412b**, and **415** was obtained. Again, *endo* selectivity was high, but attack was preferentially from the *si* face, which is less hindered if free **409d** adopts a conformation which minimizes steric interference between the propenyl side chain and the ethylene bridge of the paracyclophane substructure. Lithium benzyloxide released the auxiliary **408** and the bicyclic carboxylic acid. Reaction of **409d** with PhMgBr/CuBr led to Michael addition of a phenyl group; reaction was ≥99% *re*-face selective, and gave the adduct **411**. Hydrolysis released the carboxylic acid and **408**.[36b,151]



Scheme 92. Paracyclophane-fused oxazolone as a planar-chiral auxiliary. (i) (1) HCl, (2) $ClCO_2Et$ (30%); (ii) (1) BuLi, (2) RCH_2COCl (**409a** 95%, **409b** 95%, **409c** 93%, **409d** 94%); (iii) (from **409a** or **409b**) (1) Bu_2BOTf, Et_3N, (2) PhCHO, (3) H_2O_2 (70–75% yields); (iv) (from **409d**) PhMgBr, CuBr (85%); (v) cyclopentadiene (see text for conditions and yields).

3.11. Imidazole, [*d*]-fused

Rowlands and co-workers have prepared planar-chiral imidazoles, in a fashion analogous to the oxazolone synthesis just described. Saponification of the *o*-(*N*-arylamino) esters **416a–c**, followed by Curtius rearrangement, led to the cyclophane-fused imidazolones **417a–c**, via intramolecular capture of the intermediate isocyanates (Scheme 93). The imidazolones were converted into 2-bromoimidazoles **418a–c**, by reaction with $POBr_3$. Bromine–lithium exchange on **418a**, followed by capture with various electrophiles, allowed elaboration to **419ab** and **420**; Suzuki coupling of **418a** with benzeneboronic acid furnished **419c**. Crystal structures were obtained of **418a**, and of one diastereomer of alcohol **420**.[152] At the stage of the preliminary communication, these

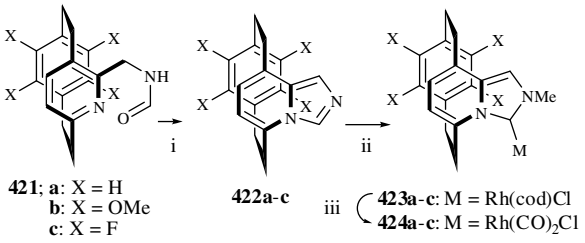


Scheme 93. Synthesis and elaboration of cyclophane-fused imidazolone. (i) (1) NaOH, H_2O/EtOH, reflux (**417a** 55%, **417b** 80%, **417c** 50%); (ii) $POBr_3$, toluene, reflux (**418a** 85%, **418b** 68%, **418c** 73%); (iii) (from **418a**) (1) *n*-BuLi, THF, −78 °C, (2) H_2O (**419a** 89%); (iv) (from **418a**) (1) *n*-BuLi, THF, −78 °C, (2) MeI (**419b** 42%); (v) (from **418a**) $Pd(PPh_3)_4$, K_2CO_3, $PhB(OH)_2$, toluene, reflux (**419c** 50%); (vi) (1) *n*-BuLi, THF, −78 °C, (2) PhCHO (61%).

reactions involved racemic material; one looks forward with interest to asymmetric versions of this chemistry.

3.12. Imidazole, [*c*]-fused

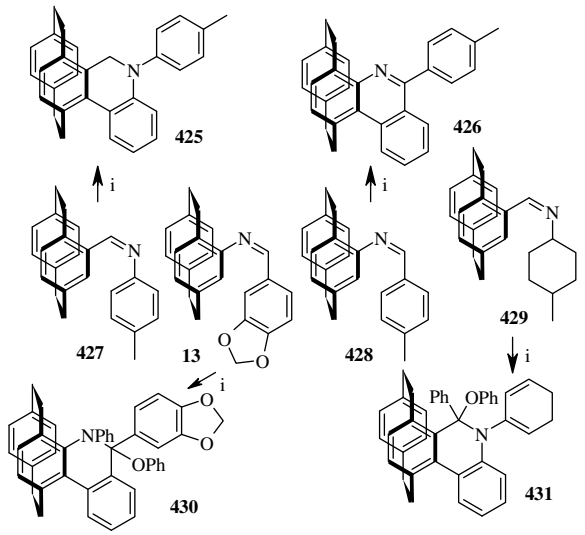
In 2007, Fürstner reported that the paracyclopyridinophane **421a** could be cyclized to the imidazole **422a**, and thence converted by standard means into the rhodium complexes **423a** and **424a** (Scheme 94). The analogues **422–424bc** were prepared in analogous fashion. The stretching frequencies of the trans-CO ligands in **424ab** were the same at ν=1989 cm^{-1}, but that of **424c** was shifted to ν=2004 cm^{-1}. Thus, remote fluorination greatly decreases the donicity of the heterocyclic carbene. The difference is electronic not steric: the crystal structures of **424a** and **424c** can be essentially overlaid.[153] Here, too, synthetic applications will be most interesting.



Scheme 94. Paracyclophane-fused *N*-heterocyclic carbene complexes. (i) $POCl_3$, toluene, 80 °C (**422a** 61%, **422b** 63%, **422c** 87%); (ii) (1) MeI, THF, 60 °C, (2) Ag_2O, CH_2Cl_2, (3) $[RhCl(cod)]_2$ (three steps: **423a** 62%, **423b** 80%, **423c** 77%); (iii) CO, THF, rt (**424a** 92%, **424b** 72%, **424c** 95%).

3.13. Quinoline and isoquinoline, [*c*]-fused

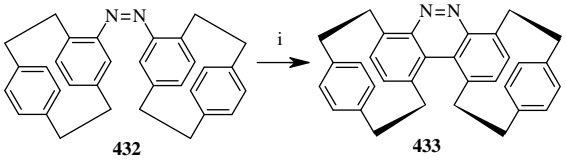
In 2001, the El-Minia and Braunschweig groups jointly reported on the reactions of [2.2]paracyclophane-bearing azomethines with benzyne (Scheme 95). Of the four imines studied, two were made from amines and [2.2]paracyclophanecarbaldehyde (**46**), and the other two from 4-amino[2.2]paracyclophane (**9**) and aromatic aldehydes. All four imines underwent [4+2] cycloaddition with benzyne, but details differed. Imine **427**, from **46** and *p*-toluidine, underwent straightforward [4+2] cycloaddition to give **425**. The reaction of **428**, from **9** and *p*-tolualdehyde, was similar, but the product aromatized in situ to give **426**. Imine **13**, from **9** and piperonal (see Section 2.10), after initial [4+2] cycloaddition, added an equivalent of water and two more equivalents of benzyne, to furnish **430**. Finally, imine **429**, from **46** and cyclohexylamine, reacted similarly to **13** and also lost two equivalents of H_2 from the cyclohexyl ring, to furnish **431**.[7]



Scheme 95. Phenanthridinophanes from Schiff bases and benzyne. (i) *o*-Benzenediazonium carboxylate, MeCN/CH_2Cl_2 (1:1), reflux, 1–2 h (**426** 22%, **426** 25%, **430** 25%, **431** 27%).

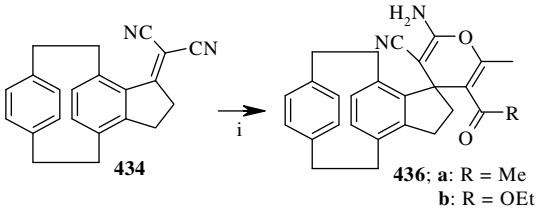
3.14. Pyridazine, [*c*]-fused; pyridine, [*b*]- and [*c*]-fused; pyran, spiro-fused

In 2003, Aly described routes to three classes of heterocycle-fused paracyclophanes. Direct irradiation of 4,4′-azobis([2.2]paracyclophane) (**432**) in the presence of $AlCl_3$ afforded **433**, in which the two paracyclophane subunits are fused to the same pyridazine ring (Scheme 96). This product was assigned as the *syn* isomer **433**, rather than an *anti* isomer, based on stabilities predicted by PM3 calculations.[154]



Scheme 96. Pyridazine fused to two [2.2]paracyclophanes. (i) *hν*, $AlCl_3$, $ClCH_2CH_2Cl$ (70%).

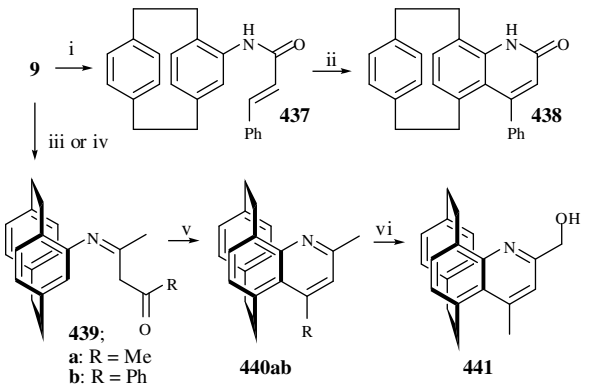
Reaction of the indanoparacyclophane **434** with acetylacetone (**435a**) or ethyl acetoacetate (**435b**) in the presence of triethylamine resulted in [3+3] condensation to afford spiro-fused pyrans **436ab** (Scheme 97). Evidently, the active methylene position of partner **435** attacks the α,β-unsaturated nitrile of **434**, and the enolate of the resulting β-dicarbonyl compound then attacks one of the nitrile groups.[154]



Scheme 97. Spiro-fused pyran on an indanoparacyclophane framework. (i) **435a**, Et_3N, EtOH, reflux (**436a** 70%) or **435b**, Et_3N, EtOH, reflux (**436b** 75%).

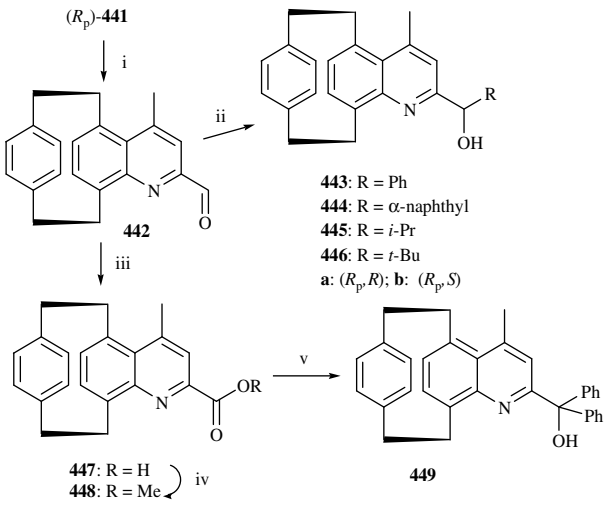
Two routes to quinolinophanes were devised. Acylation of **9** with cinnamoyl chloride gave *N*-([2.2]paracyclophan-4-yl)cinnamamide (**437**). Iodine-sensitized photocyclization then furnished the quinolinophanone **438**. Reaction of **9** with acetylacetone (**435a**) or benzoylacetone (**435b**) afforded the imines **439ab**, which were cyclized with poly-phosphoric acid to furnish the quinolinophanes **440ab** (Scheme 98).[154] This synthesis of **440a** had been discovered independently the year before, by Ruzziconi et al. They found that **440a** was metalated by butyllithium regioselectively at CH_3-2, as evidenced by oxidation with bis(trimethylsilyl)peroxide to provide **441**. By starting with resolved **10**, (R_p)- and (S_p)-**441** were available. Reaction of diethylzinc with a series of aromatic aldehydes (Eq. 2, Section 2.10) in the presence of enantiopure **441** in toluene at 20 °C led to 93–100% yields of 1-aryl-1-propanols for reaction times below about 17 h; at longer times, reduction of the arenecarbaldehyde to the corresponding arene-methanol became competitive. Enantiomeric excesses for the 1-aryl-1-propanols were 46–75%; the configuration of the new chiral center was opposite to the planar chirality of the ligand.[155] While higher asymmetric inductions have been achieved using paracyclophanes with pendant oxazoline rings (see Scheme 27, Section 2.10),[37,43] it should be noted that **441** has

planar chirality only, whereas other N,O-catalysts also have chiral centers.[155] Asymmetric inductions obtained with **441** are comparable to those obtained with oxazoline-bearing ferrocenes.[156]



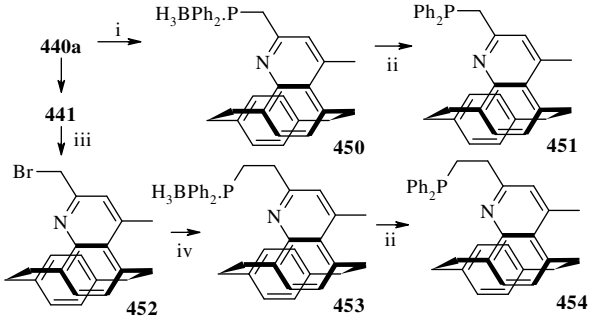
Scheme 98. Quinolinophanes from 4-amino[2.2]paracyclophane. (i) Cinnamoyl chloride, NaOH, acetone (95%); (ii) *hν*, I_2 (80%); (iii) (to **439a**) **435a**, EtOH, reflux (93%); (iv) (to **439b**) **435b**, EtOH, reflux (95%); (v) PPA, 120 °C (**440a** 75%, **440b** 80%); (vi) (from **440a**) (1) BuLi, (2) $[Me_3SiO]_2$ (79%).

To create analogues of **441** with both planar and central chirality, Ricci and Ruzziconi oxidized (R_p)-**441** to aldehyde **442** and added various Grignard reagents, providing ligands **443**–**446ab** (Scheme 99). For a ligand with steric bulk comparable to these but planar chirality only, **442** was oxidized further (H_2O_2/HOAc) to give acid **447**, which was then esterified (CH_2N_2) to **448** and treated with excess phenylmagnesium bromide, affording ligand **449**. In additions of diethylzinc to β-naphthaldehyde, the major product's absolute configuration matched that of the ligand's chiral center: (R_p,*R*) ligands gave (*R*) product, and (R_p,*S*) ligands gave (*S*) product. Ligands **443** and **444** gave 97–98% yields and 83–90% ees from either isomer; ligands **445** and **446** showed pronounced match/mismatch effects, giving 44–47% yields and 40–52% ees with the (R_p,*R*) ligands **445a** and **446a**, but 86–87% yields and 99% ees with the (R_p,*S*) ligands **445b** and **446b**. Ligand **449** gave 100% yield in 3 h, but only 67% ee, with the (*S*) product predominating. Thus, asymmetric inductions show both matching and mismatching effects between planar and central chiralities. Ligands **445b** and **446b** gave similar results on a variety of aliphatic and aromatic aldehydes.[157]



Scheme 99. Paracycloquinolinophanyl carbinols with planar and central chirality. (i) PDC (75%); (ii) RMgBr or RMgCl (**443** 53%, **a**/**b** 40:60; **444** 56%, **a**/**b** 30:70; **445** 23%, **a**/**b** 44:56; **446** 42%, **a**/**b** 46:54); (iii) H_2O_2, HCO_2H, 4 °C, 12 h; (iv) CH_2N_2, Et_2O (two steps: 82%); (v) PhMgBr, THF, 25 °C (87%).

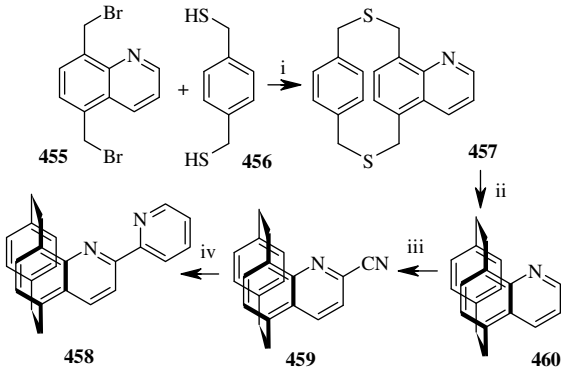
In 2007, the same group described two quinolinophane-based *P,N*-bidentate planar-chiral ligands. Metalation of (R_p)-**440a**, followed by trapping with chlorodiphenyl-phosphine and $BH_3{\cdot}OMe_2$ complex, gave the air-stable phosphine–borane complex **450**, from which ligand **451** could be released by treatment with DABCO (Scheme 100). Conversion of **441** into bromide **452** by a Cadogan reaction, followed by displacement with lithium (diphenylphosphine)methylide borane complex, gave complex **453**. Again, ligand **454** was released by treatment with DABCO. Ligands **452** and **454** were studied in the palladium-catalyzed malonylation of 1,3-diphenyl-2-propenyl acetate (Eq. 1, Section 2.10). When this reaction was catalyzed by (R_p)-**452**–Pd, **452**/Pd ratios greater than 1 gave (*R*) product predominantly, in ees up to 20%; **452**/Pd ratios *less* than 1 gave (*S*) product predominantly, in ees up to 25% at low conversion. This behavior was ascribed to competing formation of a 1:1 *P,N*-chelate and a 2:1 P,P-complex; the latter predominates at high **452**/Pd, favors (*R*) product, and is much more effective than the 1:1 P,N chelate, which presumably predominates at low **452**/Pd and favors (*S*) product. For catalysis by (R_p)-**454**-Pd, **454**/Pd ratios above 2 gave essentially racemic product; as the **454**/Pd ratio decreased from 2 to 0.5, a linear increase of the ee was observed, favoring the (*S*) product at low **454**/Pd; and a constant 56±2% ee favoring (*S*) was observed for **454**/Pd <0.5. This again was ascribed to formation of 1:1 P,N and 2:1 P,P complexes, similarly behaved to those from **451**; the **454**–Pd complex seems to be more strongly bound than the **451**–Pd complex, and hence the higher ee at low **454**/Pd.[158]



Scheme 100. Planar-chiral *P,N*-bidentate ligands. (i) (1) *n*-BuLi, (2) $ClPPh_2$, (3) $BH_3{\cdot}OMe_2$, Et_2O, 0 °C (82%); (ii) DABCO, PhH, 40° (**451** 87%, **454** 70%); (iii) CBr_4, PPh_3, Et_2O, 20 °C; (iv) $LiCH_2P(BH_3)Ph_2$, THF, −78 to 0 °C (two steps: 75%).

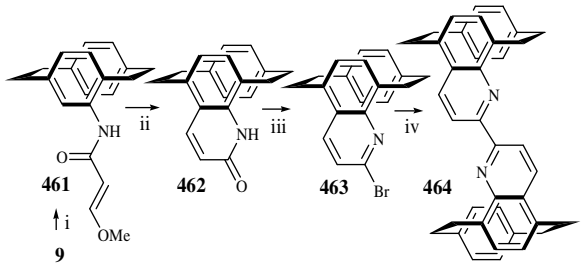
In 1999, Vögtle's group prepared the parent [2]paracyclo[2](5,8)quinolinophane (**460**) and elaborated it to a planar-chiral bipyridine (**458**; Scheme 101). High-dilution condensation of 5,8-bis(bromomethyl)quinoline (**455**) with *p*-benzenebis(methanethiol) (**456**) gave the dithiacyclophane **457** (40%); photolytic ring contraction in $P(OMe)_3$ solvent provided **460** (71%). Reissert–Henze cyanation furnished nitrile **459** (70%), the cobalt-catalyzed cyclization of which with acetylene afforded **458** (36%). Phanes **458** and **460** were resolved by chiral HPLC, and CD spectra were measured. Bipyridine **458** was studied as a ligand in copper-catalyzed cyclopropanation of styrene by ethyl diazoacetate, and in iridium-catalyzed transfer hydrogenation of acetophenone by 2-propanol (Eqs. 5 and 6, respectively, Section 2.15).[159] The systems were chosen for comparison to ligand **208**, which the same group had made earlier.[76] In cyclopropanation, **458** gave lower conversion than **208** (45% total yield vs 72%) but almost the same trans/cis ratio (2.0:1 vs 1.9:1); **458** gave a higher ee for the trans adduct (26%, vs 10% with **208**), while ee values for the cis adduct were nearly the same (26% with **458**, 23% with **208**). In transfer hydrogenation, **458** was much less active than **208** at room temperature (8% yield after 2 h, vs 49% with **208**). At 80 °C, **458** gave 93–97% yields of 1-phenylethanol in 1–2 h; **208** has not been studied at this temperature. Enantiomeric

excesses were slightly higher with **208** than with **458** (25–31% vs 18–23%), which is attributed to the chiral plane of **208** being closer to the ligating center.[159]



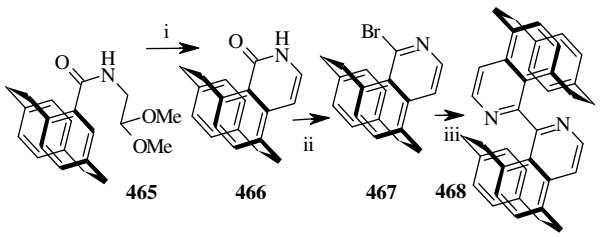
Scheme 101. Planar-chiral 2,2′-bipyridine. (i) *t*-BuOK, Cs_2CO_3, EtOH (40%); (ii) *hν* (Hg, 180 W), $P(OMe)_3$ (71%), (iii) (1) MCPBA, CH_2Cl_2, rt, (2) Me_2NCOCl, TMSCN, CH_2Cl_2, rt (70%); (iv) C_2H_2 (1.5 bar), Cp(cod)Co, toluene, 120 °C (36%).

A formal oxidative dimer of **460**, and an analogous bis(isoquinolinophane), have been prepared by Ruzziconi et al. The first two steps resemble in strategy Aly's preparation of **438** (Scheme 98), although the reagents differ. Deprotonation of (R_p)-**9** with butyllithium, followed by trapping of the resultant anion with a 3-methoxyacrylate ester (the paper is unclear whether methyl or ethyl), furnished the acrylamide **461** (Scheme 102). Acid-promoted cyclization gave quinolinophanone **462**. Treatment with $POBr_3$ converted **462** into bromide **463** (60%), the Ni^0-catalyzed homocoupling of which afforded target (R_p,R_p)-**464** (71%). Molecular mechanics calculations (MMFF94s) and NOE measurements suggest that **464** exists in a single conformation, with the phane groups *syn* and the bipyridine subunit almost exactly anti-coplanar (N–C–C–N dihedral 173°), as suggested by the drawing in Scheme 102. The optical rotation is low ($[\alpha]_D$ +36 in THF, −10 in $CHCl_3$), which the CD spectrum shows to arise from a series of positive/negative Cotton effects of similar intensity down to 240 nm.[160]



Scheme 102. (R_p,R_p)-2,2′-Bis{[2]paracyclo[2](5,8)quinolino-phane}. (i) (1) *n*-BuLi, (2) MeOCH=$CHCO_2R$, THF, rt; (ii) concd HCl (two steps: 40%); (iii) $POBr_3$, 120 °C, 1.5 h (60%); (iv) $NiCl_2{\cdot}6H_2O$, PPh_3, Zn, DMF, 50 °C, 1 h (71%).

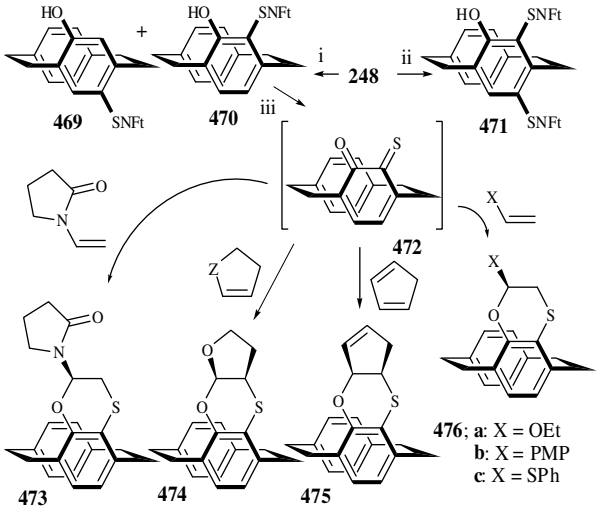
Preparation of the bis(isoquinolinophane) analogue **468** began with the amide **465**, derived from (R_p)-[2.2]paracyclophane-4-carbonyl chloride [(R_p)-**44**] and aminoacetaldehyde dimethyl acetal (Scheme 103). Cyclization of **465** (PPA) gave isoquinolinophanone **466** (47%). From this point, the synthesis parallelled that of **464**: treatment with $POBr_3$ furnished bromide **467** (45%), and Ni^0-catalyzed homocoupling provided **468** (43%). NOE measurements indicate that, in the predominant conformation of **468**, the isoquinoline substructures have a large dihedral angle and a chirality about the central axis of S_a. Molecular-mechanics calculations are consistent with the same conclusion, predicting an N–C–C–N dihedral of 72°. Unlike **464**, **468** has very large optical rotations: $[\alpha]_D$ +468 in $CHCl_3$, +556 in MeOH, +437 in MeCN. The CD spectrum shows dominance by positive Cotton effects.[160]



Scheme 103. (R_p,R_p)-1,1′-Bis{[2]paracyclo[2](5,8)-isoquino-linophane}. (i) PPA, 110 °C, 30 min (47%); (iii) $NiCl_2{\cdot}6H_2O$, PPh_3, Zn, DMF, 50 °C, 1 h (43%).

3.15. 1,4-Oxathiane, [*b*]-fused

In 2006, the groups of Menichetti and Minuti reported that sulfenylation of 4-hydroxy[2.2]paracyclophane (**248**) with phthalimide-sulfenyl chloride (FtNSCl) gave a 2:3 mixture of the *p*- and *o*-sulfenylated derivatives **469** and **470** (Scheme 104), from which **470** could be isolated. Sulfenylation with excess FtNSCl furnished the bis-sulfenyl product **471**. Deprotonation of **470** with triethylamine in the presence of electron-rich alkenes gave Diels–Alder adducts of *o*-monothioquinone **472**. Adducts **473**–**476** were obtained in 60–97% yields, with complete regio- and stereo-selectivity.[161]

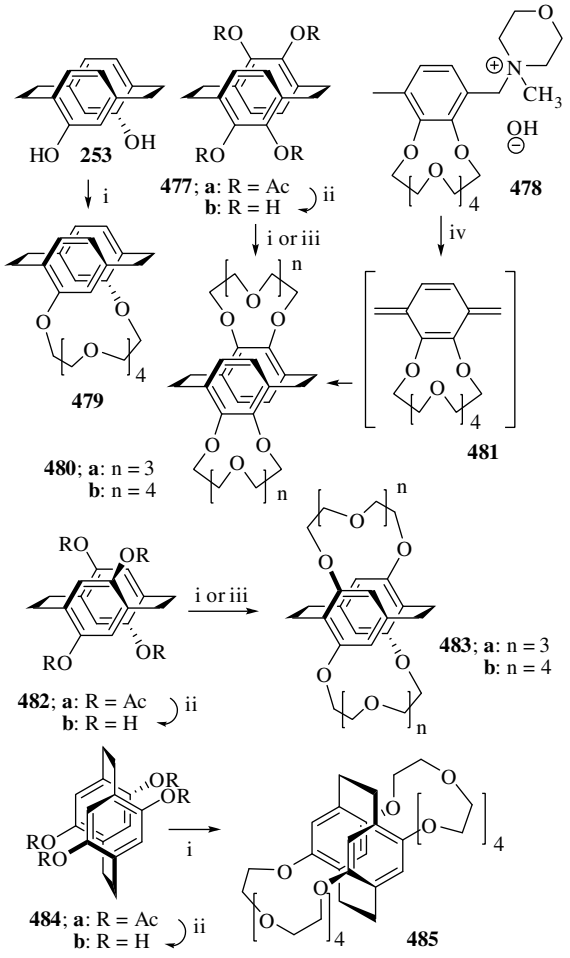


Scheme 104. Diels–Alder adducts of paracyclophane-*o*-monothioquinone. (i) FtNSCl (1 equiv), $CHCl_3$, 0 °C, 2 h (**469**/**470**=2:3, **470** isol. 58%); (ii) FtNSCl (2.2 equiv), $CHCl_3$, rt, 2 h (82%); (iii) (from **470**) Et_3N (1 equiv), dienophile (2–5 equiv), $CHCl_3$, 60 °C, 20 h (**473** 77%, **474** 90%, **475** 92%, **476a** 86%, **476b** 97%, **476c** 60%).

3.16. Crown ether

In 1974, Cram's group described the preparation of [2.2]paracyclophanes fused to crown ether systems. In some of these structures, the crown is fused to the paracyclophane subunit, like the other systems in this section; in others, one or more polyether bridges connect the two rings of the paracyclophane. For comparison, all are treated here. Five structures were prepared (Scheme 105). Treatment of [2.2]paracyclophane-4,12-diol (**253**) with pentaethylene glycol dichloride and KOH gave **479**. Tetraacetates **477a**, **482a**, and **484a** were reduced with $LiAlH_4$ to furnish tetrols **477b**, **482b** and **484b** respectively; without purification, the tetrols were subjected to tetra- or pentaethylene glycol dichloride and KOH, to provide macrocycles **480ab**, **483ab**, and **485**. Yields were lower for the crown-5 derivatives **480a** and **483a**, than for the crown-6 derivatives **479**, **480b**, **483b**, and **485**.[162,163] This trend would be expected if the transition state involves K^+ acting as template for the glycol dichloride, which would favor formation of a crown-6,

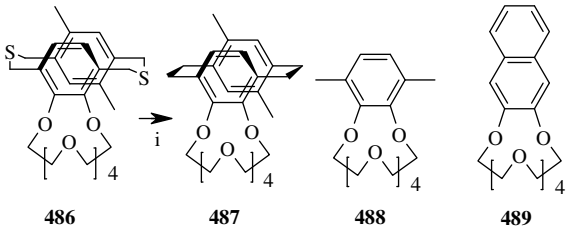
but provide less assistance to an incipient crown-5. Another synthesis of **480b** involves dimerization of *p*-phenylene-18-crown-6 (**481**), generated by Hofmann elimination of **478.**[163]



Scheme 105. Preparation of crown-fused [2.2]paracyclophanes. (i) $Cl(CH_2CH_2O)_4$-CH_2CH_2Cl, *n*-BuOH, KOH, reflux, 24 h (**479** 18%, **480b** 14%, **483b** 25%, **485** 23%); (ii) $LiAlH_4$; (iii) $Cl(CH_2CH_2O)_3CH_2CH_2Cl$, *n*-BuOH, KOH, reflux, 24 h (**480a** 6%, **483a** 3%); (iv) (to **480b**) toluene, reflux ($-H_2O$), phenothiazine (10%).

These compounds were prepared as part of an extensive study of the relation between the structure of polyether hosts, and their binding constants with ammonium guests. Hosts **480b**, **483b**, and **485** would solubilize 2 equiv of *t*-$BuNH_3^+BPh_4^-$ in $CDCl_3$, in which the salt was insoluble without host. Host **480b** formed a crystalline 1:2 complex with *t*-$BuNH_3^+SCN^-$ and 1:1 complexes with hexamethylenediammonium or decamethylenediammonium hexafluorophosphates.[164] In chloroform at 24 °C, binding constants (*K*) for *tert*-butylammonium ion were as follows: 18-crown-6, 7.5×10^5; **479**, 40; **480a**, 1.6×10^2; **480b**, 3.1×10^2; **483a**, <40; **483b**, 1.6×10^2; and **485**, 5.0×10^1. The decrease in *K* versus 18-crown-6 was attributed to the oxygens being held in non-optimal binding arrangements, the aryl oxygens being held too far apart (in **479**, **483b**, and **485**) for best binding, steric hindrance with the cyclophane system, and (in **480b**) all six oxygens not being involved in binding, as suggested by the binding constant being close to that of **480a**.[163,164] Binding-constant trends with alkali-metal or ammonium ions parallelled those with *tert*-butyl-ammonium ion.[163] Crystal structures have been obtained of the free hosts **480b** and **485**.[165]

To examine the substituent effects on binding by crown-6 systems, in 1983 Bell, Cram, et al. prepared host **487** (Scheme 106). The dithia[3.3]cyclophane **486**, which had been made by the classic Cram–Boekelheide method, was oxidized with MCPBA to furnish the disulfone (95%), which upon photolysis extruded SO_2 to give **487** (83%). Binding by **486** and **487** was compared to binding by **480b** and models **488** and **489**. Binding of alkali-metal, ammonium, and alkylammonium cations descended in the following order: **489**>**480b**>**487**>**488**=**486**. This order could not be correlated with general steric bulk, since the cyclophanes (**480b**, **486**, **487**) are larger than the non-cyclophanes (**488**, **489**), but there seemed to be specific host–guest repulsion in the [2.2]paracyclophanes **480b** and **487**.[166]



Scheme 106. Dimethylated [2.2]paracyclophano-18-crown-6 and models. (i) (1) MCPBA (95%), (2) *hν* (83%).

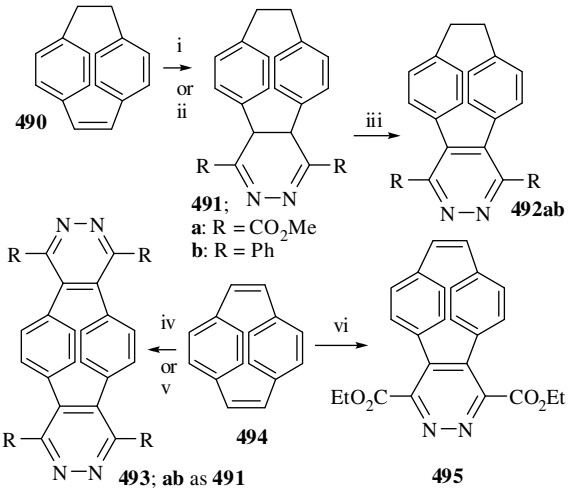
4. Heterocycle pendant from spanning bridge

To the best of our knowledge, there are no known [2.2]paracyclophanes with heterocyclic rings pendant from the spanning bridge. Such compounds should be accessible: the spanning bridges of [2.2]paracyclophane have been functionalized by several groups, although not with heterocycles.[36a,38,44,45,167] Compounds of type C stand as open invitations to chemical creativity.

5. Heterocycle fused to spanning bridge

5.1. Pyridazine, [*d*]-fused

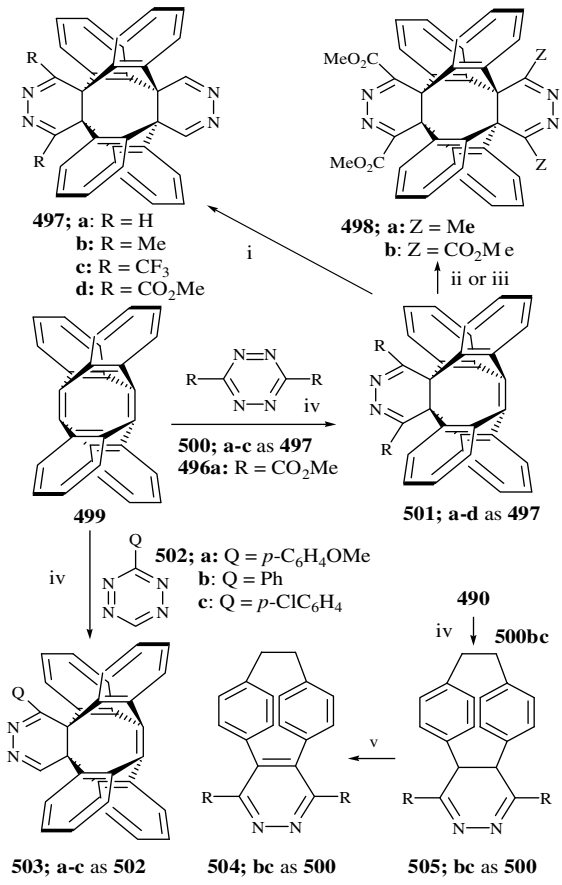
In 1992, de Meijere and König reported that reaction of paracyclophene **490** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**496a**; see Scheme 108 for structure) in chloroform at room temperature provided a mixture of adduct **491a** and a tautomer derived by 1,3-hydrogen shift (Scheme 107); the sequence of events is presumably Diels–Alder cycloaddition followed by loss of dinitrogen. DDQ oxidation then gave pyridazine **492a** (Scheme 107), the structure of which was confirmed crystallographically. Reaction



Scheme 107. Reaction of paracyclophene and paracyclophadiene with tetrazines. (i) **496a**, $CHCl_3$, rt (**492a** 85%); (ii) **496b**, xylene, reflux (**492b** 91%); (iii) DDQ (**492a** 91%); (iv) (1) **496a** (2 equiv; 80%), (2) DDQ (**493a** 61%); (v) **496b** (2 equiv; **493b** 33%); (vi) (1) **496a** (1 equiv; 59%), (2) DDQ (74%).

of **490** with 3,6-diphenyl-1,2,4,5-tetrazine (**496b;** same as **496a**, but R=Ph) would take place only in refluxing xylene; autoxidation occurred in situ to furnish **492b** directly. Reactions of **496ab** with [2.2]paracyclopha-1,9-diene (**494**) took place under the same conditions as with **490**; excess **496ab** gave adducts **493ab**, while a single equivalent of **496a** furnished mono-adduct **495**. Since **490** is strained but sterically hindered, its rate of reaction with **496a** was compared with that of other dienophiles; **490** reacted with **496a** 140-fold faster than did 1,1-diphenylethene, but 18-fold more slowly than did styrene, and three to four *orders of magnitude* more slowly than cyclopentene or norbornene; that is, the strain seems to be less important than the hindrance.[168,169]

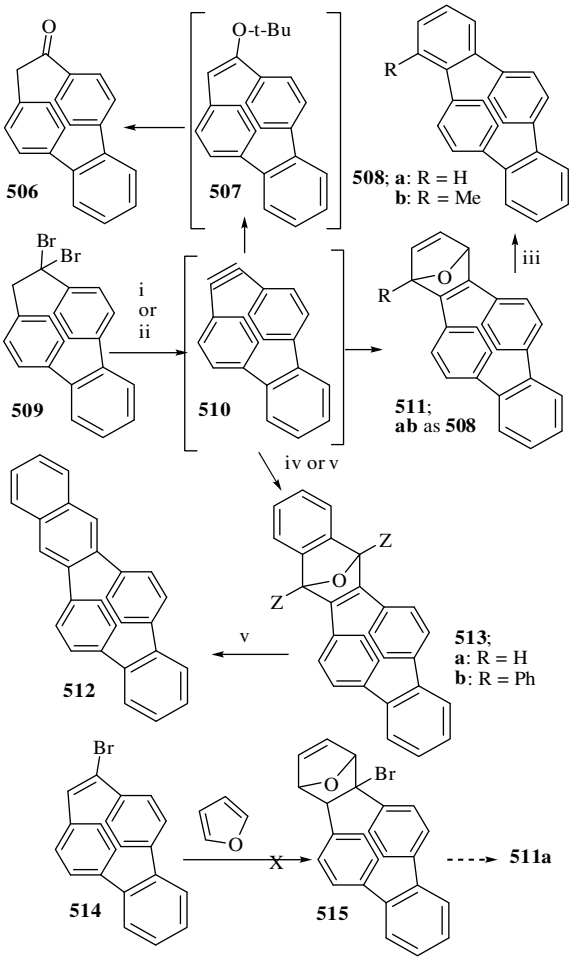
Tetradehydrodianthracene **499**, which contains [2.2]paracyclophane-1,9-diene substructures, reacted with tetrazines **500a–c** and **496a** to give 1:1 adducts **501a–d** (Scheme 108). Adducts **501a–d** would react with the parent tetrazine (**500a**) at 20 °C and 1 atm to furnish 2:1 adducts **497a–d**. The 1:1 adduct **501d** would enter into further cycloaddition with **496a** or **500b**, but only at 50 °C and 4 kbar pressure, to afford adducts **498ab**. The observed order of reactivity towards **499**, viz. **500a**>**500b**>**500c**, is the reverse of expectation for an inverse electron-demand Diels–Alder reaction, and was attributed to steric hindrance. Two tests of this hypothesis were devised. The reaction of **499** with mono-aryltetrazines **502a–c** gave 1:1 adducts **503a–c**; the idea here was to vary the electron demand of the tetrazine with constant steric bulk. Reactivity followed the order: **503a**<**503b**<**503c**, as expected in an inverse electron-demand Diels–Alder reaction. Reaction of de Meijere's dienophile **490** with **500bc** gave adducts **505bc**, and thence by oxidation **504bc**; these experiments were designed to test reactivity towards a less hindered dienophile than **499**. Reactivity followed the order: **500b**>**500c**>**496a**, and **500a** would not react under the test conditions; this is the order expected, and was taken to confirm that the unusual reactivity towards **499** reflected steric hindrance.[170]



Scheme 108. Reactions of tetradehydroanthracene with tetrazines. (i) **500a**, CH_2Cl_2, 20 °C, 1 bar; **497a** (90%), **497b** (92%), **497c** (88%), **497d** (99%); (ii) (from **501d**) **500b**, CH_2Cl_2, 50 °C, 4 kbar, 15–20 h (**498a** 96%); (iii) (from **501d**) **496a**, CH_2Cl_2, 50 °C, 4 kbar, 15–20 h (**498b** 66%); (iv) 20 °C, CH_2Cl_2; **501a** (54%), **501b** (77%), **501c** (54%), **501d** (37%), **503a** (63%), **503b** (75%), **503c** (88%), **505b** (92%), **505c** (96%); (v) DDQ; **504b** (100%), **504c** (83%).

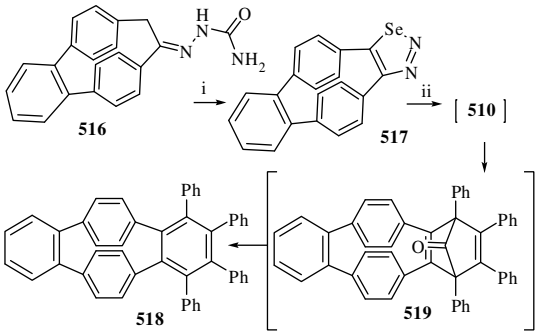
5.2. Furan, [*c*]-fused; 1,2,3-selenadiazole, [*d*]-fused

Another route to bridge-fused [2.2]paracyclophanes involves the intermediacy of [2.2]paracycloph-1-ynes. In 1988, Chan and Wong reported than dehydrobromination of *gem*-dibromide **509** with excess *tert*-butoxide in the presence of a furan or isobenzofuran gave **511ab** and **513ab**, the adducts expected from Diels–Alder trapping of cyclophyne **510** (Scheme 109). Ketone **506**, presumed to arise by hydrolysis of the *tert*-butoxide trapping product **507**, was also isolated. Reductive deoxygenation of **511ab** or **513a** afforded the corresponding carbocycles **508ab** or **512**, although **513b** resisted deoxygenation. Since paracyclophyne **510** could not be observed directly, several indirect tests for its intermediacy were performed. An alternative route to **511a** would involve cycloaddition of furan with vinyl bromide **514**, the adduct (**515**) then eliminating HBr to give **511a**. Authentic **514** would not cycloadd with furan under the reaction conditions, thus disproving the hypothesis.[171]



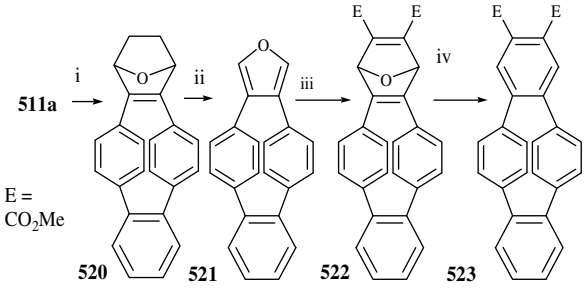
Scheme 109. Generation and trapping of a 1-paracyclophyne. (i) *t*-BuOK, furan, THF: (**511a** 47%, **506** 21%); (ii) *t*-BuOK, 2-methylfuran, THF: (**511b** 11%, **506** 12%); (iii) $TiCl_4$, $LiAlH_4$, Et_3N, THF: (**508a** 72%, **508b** 93%); (iv) (to **513a**) isobenzofuran, *t*-BuOK, THF, rt (74%); (v) (to **513b**) diphenylisobenzofuran, *t*-BuOK, THF, rt (40%); (v) (from **513a**) $TiCl_4$, $LiAlH_4$, Et_3N, THF (77%).

In order to generate authentic **510** by thermolysis of a 1,2,3-selenadiazole, semicarbazone **516** (from ketone **506**) was oxidized with SeO_2 to give **517** (Scheme 110). Pyrolysis of **517** at 220 °C in DMSO containing tetraphenylcyclopentadienone furnished the tetraphenyl-dibenzoparacyclophane **518**, presumably via **510** and initial adduct **519**. This result was taken to confirm the existence and dienophilicity of **510**.[171]



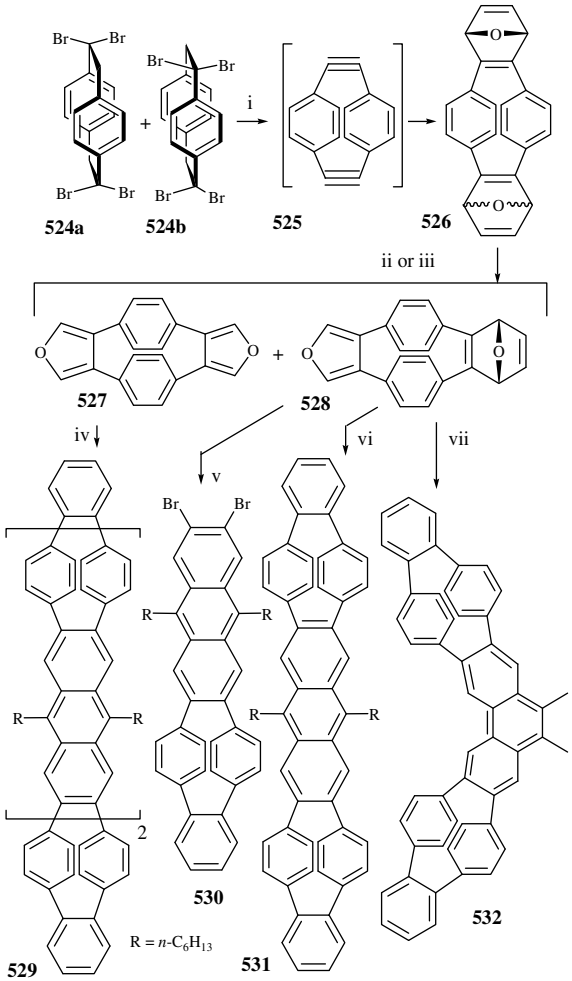
Scheme 110. Generation of a 1-paracyclophyne from a 1,2,3-selenadiazole. (i) SeO_2, dioxane, 80 °C (50%); (ii) 220 °C, DMSO, tetraphenylcyclopentadienone (8%).

To access a differently substituted dibenzoparacyclophane, **511a** was hydrogenated to give **520** regioselectively (Scheme 111). Heating of **520** to 220 °C at 0.5 Torr led to retro-Diels–Alder extrusion of ethylene and formed benzofuroparacyclophane **521**. Heating of **521** with excess DMAD in toluene afforded adduct **522**, the reductive deoxygenation of which provided **523**.[171]



Scheme 111. Generation and elaboration of a benzofuro-paracyclophane. (i) H_2, Pd/C, PhH/EtOH (97%); (ii) 220 °C, 0.5 mmHg (92%); (iii) DMAD, toluene, reflux (83%); (iv) $TiCl_4$, $LiAlH_4$, Et_3N, THF (70%).

In 1991, de Meijere's group reported that dehydrobromination of a mixture of 1,1,9,9- and 1,1,10,10-tetrabromo[2.2]paracyclophanes (**524ab**) with *tert*-butoxide in the presence of furan furnished (23%) a mixture of *anti*- and *syn*-**526**, formally via [2.2]paracyclopha-1,9-diyne (**525**; Scheme 112). Flash vacuum pyrolysis (FVP) of **526**, at 240 °C and 2 mbar pressure, afforded 1:2,9:10-bis(3,4-furano)-[2.2]paracyclophane (**527**) in 60% yield via extrusion of two molecules of ethyne. FVP of **526** at 0.01 mbar, corresponding to a shorter contact time in the hot tube, provided a separable mixture of **526** (20%), **527** (34%), and **528** (27%). The furan rings of **527** and **528** acted as Diels–Alder dienes toward assorted arynes and bisdehydroarenes ('arene-diynes'); the initial adducts, which existed as mixtures of stereoisomers, were deoxygenated with $LiAlH_4/TiCl_4$ to release the arene-fused paracyclophanes **529**–**532**. These will be recognized as small rigid rods with alternating mutually orthogonal aromatic subunits.[169,172]



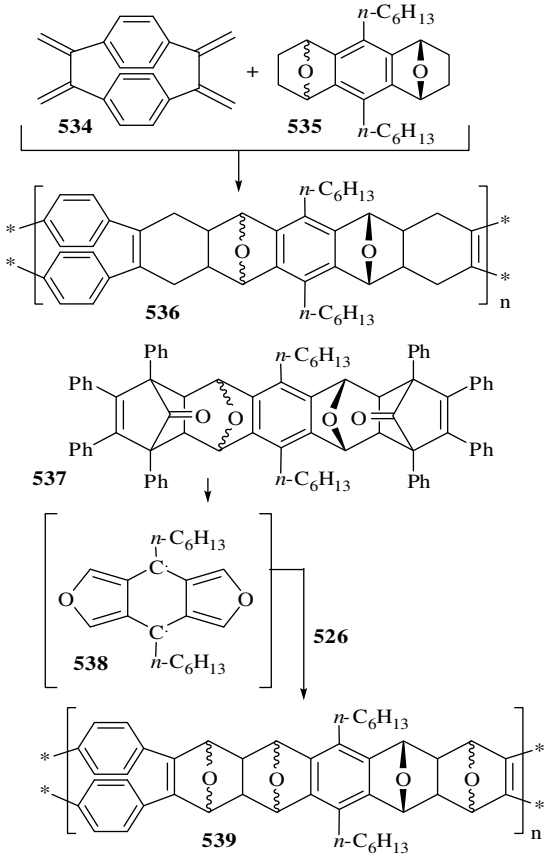
Scheme 112. Furan adducts of [2.2]paracyclopha-1,9-diyne. (i) *t*-BuOK, furan; 23%; (ii) 240 °C, 2 mbar: **527** (60%); (iii) 240 °C, 0.01 mbar: **526** (20%), **527** (34%), **528** (27%); (iv) (1) **530** (2.5 equiv), *n*-BuLi (2.7 equiv); (2) $TiCl_4$, $LiAlH_4$ (18%); (v) (1) 1,2,4,5-tetrabromo-3,6-dihexylbenzene (**533**; 1 equiv), *n*-BuLi (1.1 equiv), (2) $TiCl_4$, $LiAlH_4$ (40%); (vi) (1) **533** (0.5 equiv), *n*-BuLi (1.1 equiv), (2) $TiCl_4$, $LiAlH_4$ (25%); (vii) (1) 1,2,3,4-tetrabromo-5,6-dimethylbenzene (0.5 equiv), *n*-BuLi (1.1 equiv), (2) $TiCl_4$, $LiAlH_4$ (15%).

To prepare even longer rigid-rod molecules with similar subunits, a polymerization approach was adopted. Heating of 1,2,9,10-tetramethyleneparacyclophane (**534**) with the bis(oxanorbornadiene) **535** in xylene furnished oligomer **536** (n=16; Scheme 113). Similarly, heating of **537** releases the highly reactive **538**; if this was done in the presence of **526**, the oligomer **539** was produced (n=7). Reductive deoxygenation of both **536** and **539** failed, however, due to the very low solubility of partly reduced products.[169]

6. Heterocycle bridging the two benzene rings

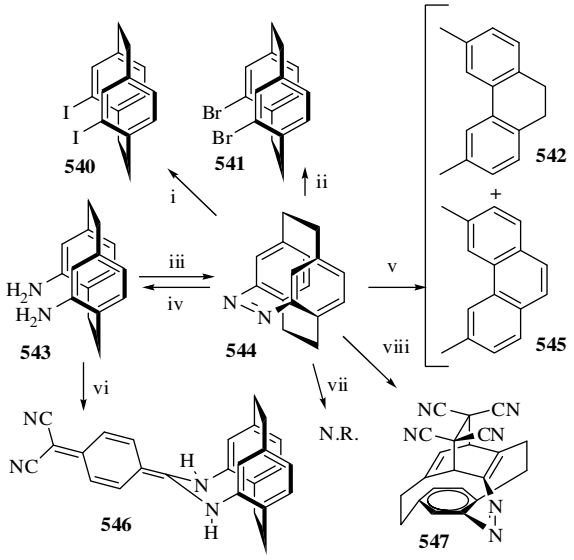
A few examples are discussed above (Section 2.15).[70]

In 2003, Hopf et al. reported that hypochlorite oxidation of 4,13-diamino[2.2]-paracyclophane (**543**) created the azo-bridged cyclophane **544** (Scheme 114). The crystal structure of **544** revealed strain: the N=N bond length was 1.272 Å, vs a standard X-ray value of 1.255 Å, and the bridge C–C bond lengths were longer than in [2.2]paracyclophane. The benzene rings retain a flattened boat shape. Reduction of **544** with zinc in acetic acid re-converted it into **543**; iron and bromine produced dibromide **541**; and iodine monochloride in acetic acid furnished diiodide **540**. Pyrolysis of **544** led to decomposition only above 450 °C; at that temperature the products isolated were **542** and **545**, each in a small quantity. They



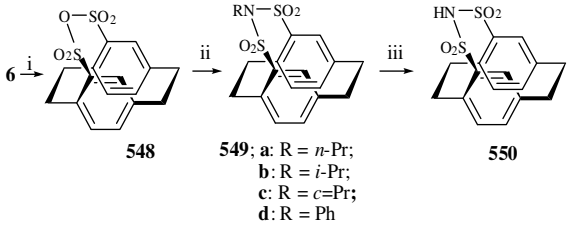
Scheme 113. Extended rigid-rod molecules with paracyclophane subunits. Yields not stated.

appeared to form by (1) de-azotization; (2) bridge scission; (3) *ortho* re-closure; and (4) hydrogen shift. Exposure to aluminum chloride led to recovery of starting material, not to rearrangement, but **544** underwent Diels–Alder reaction with tetracyanoethylene, to furnish adduct **547**.[173] Later, the El-Minia and Braunschweig groups studied charge-transfer reactions of diamine **543** with various π-acceptors; with 7,7,8,8-tetracyanoquino-dimethane (TCNQ), the bridged heterocycle **546** was obtained.[174]



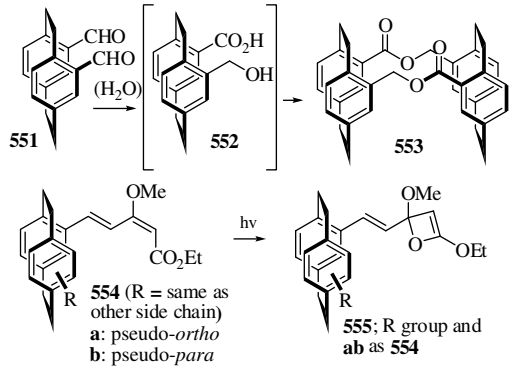
Scheme 114. Formation and reactions of azo-bridged paracyclophane. (i) ICl, HOAc (22%); (ii) Fe, Br_2 (64%); (iii) NaOCl, NaOH (98%); (iv) Zn, HOAc (76%); (v) >450 °C (1.5% each **542** and **545**); (vi) TCNQ (65%); (vii) $AlCl_3$; (viii) TCNE (54%).

Cerfontain's group has reported that [2.2]paracyclophane (**6**) can be sulfonated to the 4,13-disulfonic anhydride **548** either with 4.0 equiv of SO_3[140b,175] or with chlorosulfuric acid (Scheme 115).[176] Reaction of **548** with primary amines followed by P_2O_5 provides the *N*-alkyldisulfonimides **549**; the list shown is non-exhaustive. Pyrolysis of **549a–c** at 200 °C gave the parent imide **550**.[140b,176] Crystal structures of **548**, **549a–d**, and **550** have been obtained.[177]



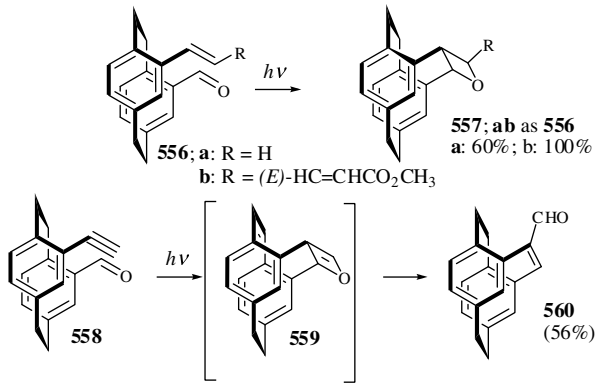
Scheme 115. [2.2]Paracyclophane-4,13-disulfonic anhydride and -disulfonimides. (i) SO_3 (87%) or $ClSO_3H$ (97%); (ii) (1) RNH_2, (2) P_2O_5 (up to 56% for **549a**); (3) (from **549a–c**) 200–210 °C, 20 min (>95%).

The isolation and storage of 4,13-[2.2]paracyclophanedicarbaldehyde (**551**) are notoriously difficult, because it undergoes an internal Cannizzaro reaction to give **552.** In 2005, Hopf and coworkers reported the isolation of bis-lactone **553** (Scheme 116), and obtained a crystal structure. In the same study, solid-state irradiation of vinylogous cinnamates **554ab** (prepared by Wittig–Horner olefination of the corresponding dialdehydes) furnished small amounts of oxetenes **555ab**.[178]



Scheme 116. Heterocycles in the cinnamophane vinylogue series. Yields of **553** and **555a** not stated; **555b** unstable.

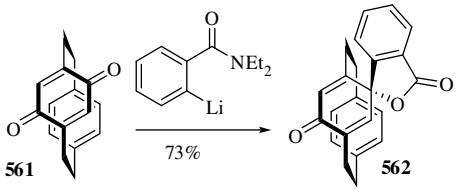
The solution-phase photochemistry of [2.2]paracyclophanes bearing unsaturated groups pseudo-geminally positioned, is dominated by [2+2] cycloadditions between the side chains, several of which form heterocycles (Scheme 117). Vinyl aldehydes **556ab** give



Scheme 117. Transannular photochemistry in pseudo-geminally substituted cyclophanes.

oxetanes **557ab**, respectively, and alkynyl aldehyde **558** gives [2.2.2](1,2,4)cyclophene-carbaldehyde **560**, presumably from electrocyclic opening of oxetene **559**. It was hoped that dialdehyde **551** would afford a dioxetane, but under the conditions only slow decomposition occurred.[179]

Finally, there is an example of a [2.2]paracyclophane skeleton with a spiro-fused heterocycle attached. In 2005, Rozenberg reported that reaction of [2.2]paracyclophane-4,7-quinone (**561**) with excess {*o*-[(diethylamino)carbonyl]phenyl}lithium furnished the spirocyclic lactone **562** (Scheme 118).[180]



Scheme 118. Spirocyclic lactone from paracyclophane monoquinone.

7. Summary

Many heterocyclic systems based on [2.2]paracyclophane have been prepared, mostly by adapting standard heterocyclic syntheses to paracyclophane-based substrates, but some by utilizing the unusual steric hindrance or transannular interactions of the paracyclophane substructure. As stated at the outset, the resulting structures are interesting and useful, particularly for their planar chirality and deck-to-deck electronic communication. The field is far from mature; most of the discussions herein describe just a preparation or two, from which it follows that far more remains to be discovered.

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