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Iptycenes, cuppedophanes and cappedophanes

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ABSTRACT

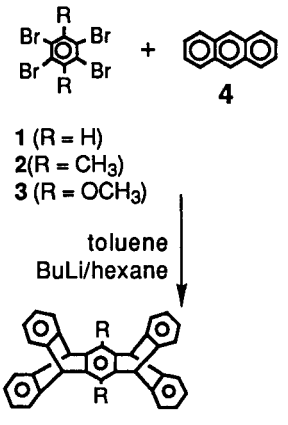
Iptycenes are extended triptycenes. They have attractive rigid frameworks, often with intramolecular cavities, and show exceptional thermal stability. The rapid assembly of iptycenes such as **5**, **22**, **28**, **31** and **37**, mainly via cycloaddition reactions, is described. Cuppedophanes and cappedophanes are novel cyclophanes that can be quickly constructed via a tandem aryne–nucleophilic addition sequence. Examples whose synthesis and properties are described include **54**, **57**, **60** and **65-67**.

INTRODUCTION

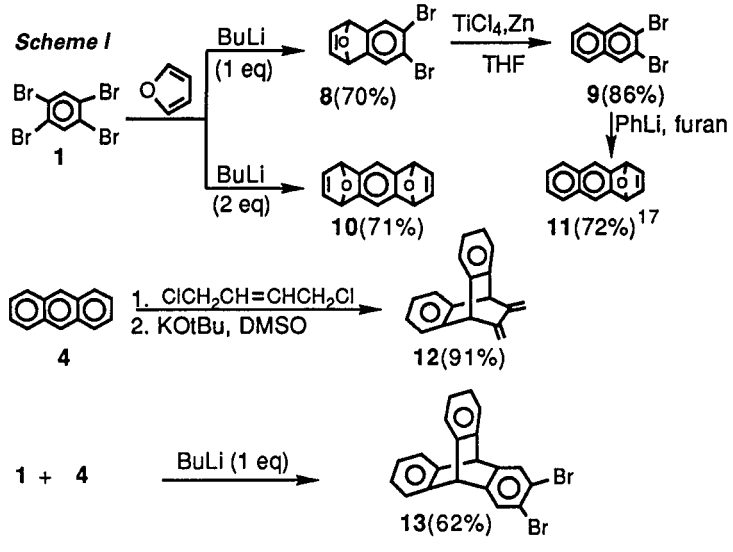
Some years ago we became interested in extending the chemistry of arynes (dehydrobenzenes)[1] to situations in which more than one aryne intermediate might be formed simultaneously or successively on a single aromatic ring.[2,3] It was our hope that this type of methodology would permit the rapid elaboration of a single aromatic ring into a more complex structure in a one-pot operation. The classes of compounds mentioned in the title arose naturally from these studies.

IPTYCENES

It is somewhat surprising that it was not until just over a decade ago that it was realized[4,5] that triptycene is the parent of a large, interesting and synthetically challenging class of compounds based on one or more triptycene subunits.[6] Since these molecules have more than three independent benzenoid planes, we coined the general name 'iptycenes',[4] with the prefix indicating the number of such planes (three for triptycenes; five for pentiptycenes, and so on). For example, our one-step synthesis of pentiptycene **5** followed Wittig's original triptycene synthesis, but used 1,2,4,5-tetrabromobenzene as a diaryne equivalent.[4] Analogues **6** and **7** were similarly prepared.[4]



5 (R = H) 26%, mp 483 °C
6 (R = CH_3) 35 %, mp 460-462 °C
7 (R = OCH_3) 37%, mp 400-402 °C

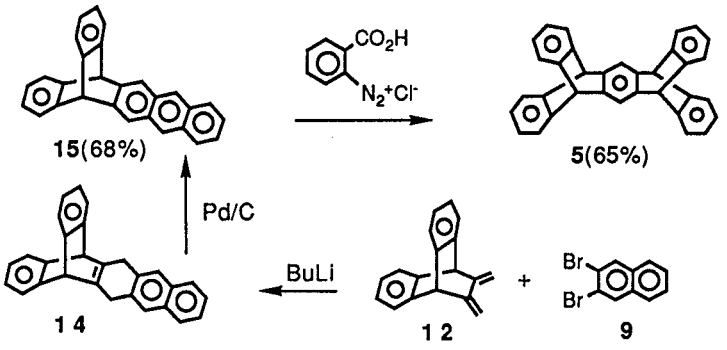


DEVELOPMENT OF OTHER IPTYCENE SYNTHONS

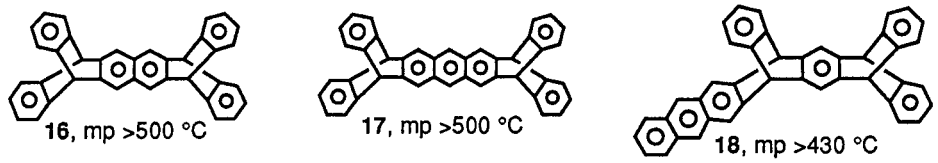
Although the above route to pentiptycenes is short, it is not without problems. For example the yield of **5** is high (94%) based on consumed anthracene, but an excess of anthracene must be used and its separation from the pentiptycene is tedious; the yield based on tetrabromobenzene is only 26%. Consequently, we devised and prepared an array of iptycene synthons, all of which could be prepared in good yield and multigram quantities, as shown in Scheme I. Using aryne and Diels-Alder chemistry, these synthons (and a few others, described below)

can be combined to produce a variety of iptycenes. For example, pentiptycene **5** can be prepared in 65% yield by addition of benzyne to triptycene **15**; this, in turn, can be prepared by four short routes from the synthons in Scheme I[5,7], one of which is shown in Scheme II.

Scheme II

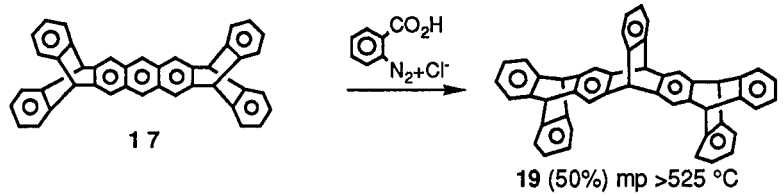


Similar methodology has been applied to the synthesis of pentiptycenes with fused acene rings, such as **16-18**.[5]



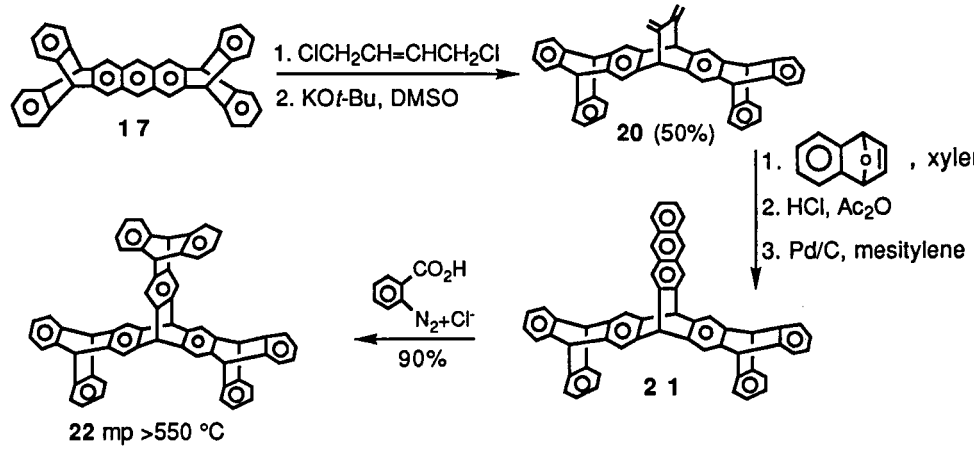
HEPTIPTYCENES AND NONIPTYCENES

The anthracene rings in **17** and **18** can be further elaborated to construct higher iptycenes. For example, addition of benzyne to **17** (or **18**) gives heptiptycene **19**.[7]



Elaboration of pentiptycene **17** to noniptycene **22** (trivially called tritriptycene[8]) has been accomplished as illustrated in Scheme III.

Scheme III[8,9]



Noniptycene **22** has the molecular formula $C_{62}H_{38}$, but the D_{3h} symmetry reduces the NMR spectra to just 8 unique carbon and 5 unique proton signals.

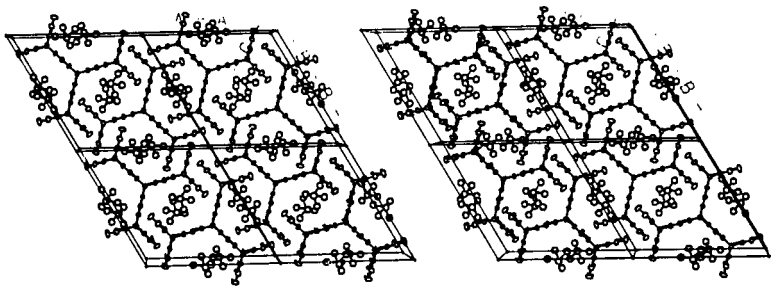


Figure 1. Stereoview of the packing pattern of the 1:1 tritriptycene: acetone complex.

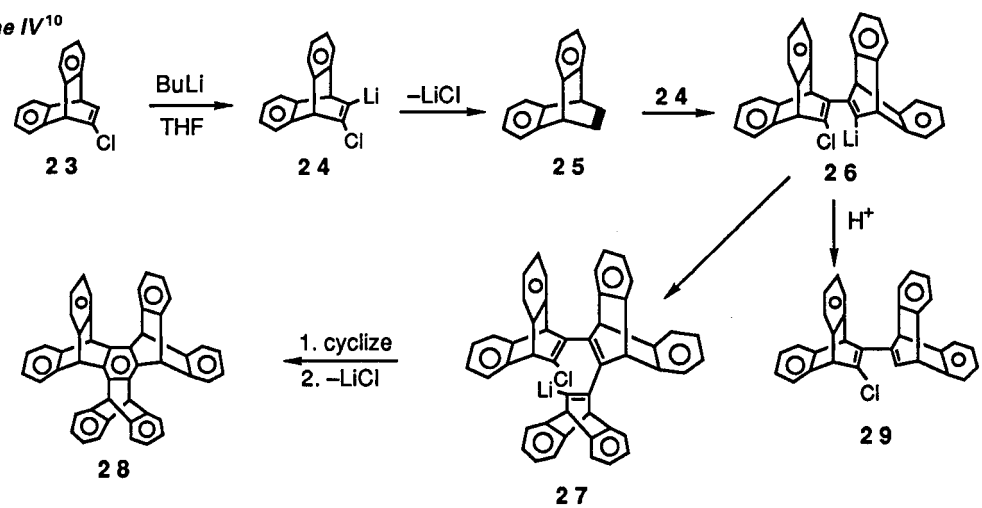
Iptycene **22** has three equivalent U-shaped cavities which can accomodate small guest molecules. Figure 1 shows the packing pattern in a crystal of the 1:1 complex of **22** with acetone. On an average only 1/3 of the cavities are filled, and the positional disorder of the acetone molecules refined to two molecules whose planes are orthogonal but with a common position for the carbonyl group. The channel nature of the complex is clear from the figure.

THE BICYCLOALKYNE TRIMERIZATION ROUTE TO IPTYCENES

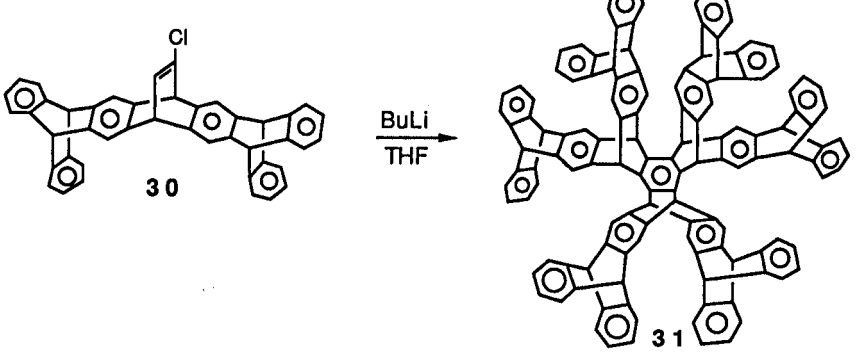
A centrosymmetric class of iptycenes with a benzenoid ring at the center can be synthesized in one operation through the 'trimerization' of a vinyl chloride. The reaction proceeds stepwise via a bicycloalkyne intermediate, as illustrated for **28**[10,11] in Scheme IV. The presence of each intermediate (**24-27**) has been established by trapping experiments.[10] By appropriate choice of solvent the reaction can be stopped at 'dimer' **26**, so that chlorodiene **29** and its reduction product **32**, both useful iptycene synthons, [12,13] can be obtained in high yield.

The trimerization methodology has been extended to higher homologs (Scheme V[14]). CPK models of nonadecaiptycene **31** are shown in Figure 2. This $C_{132}H_{78}$ hydrocarbon, which has only 12 magnetically unique carbons and 5 unique protons, is the largest monomeric iptycene synthesized to date.

Scheme IV[10]



Scheme V[14]



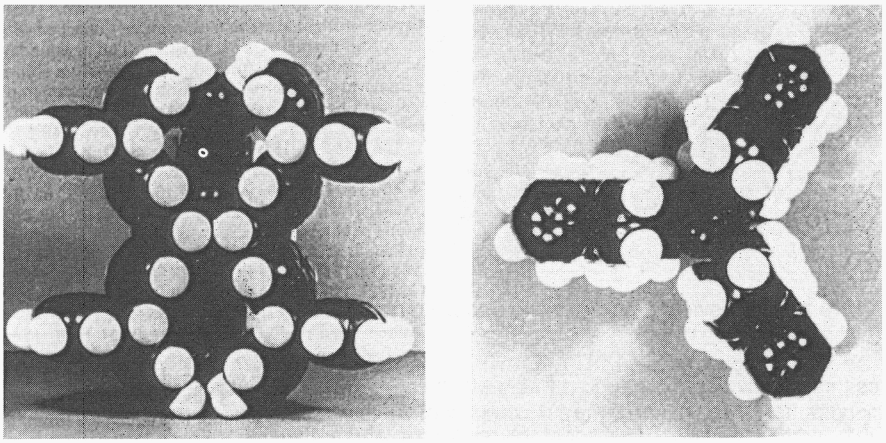
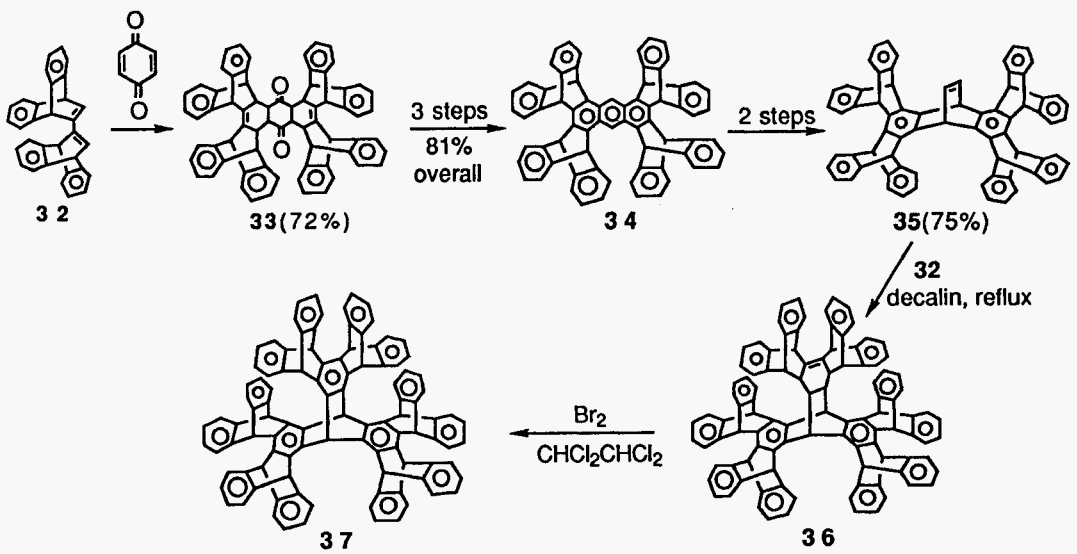


Figure 2. CPK models of 31: side view showing cavities above and below the central benzene ring (left), and top view looking into one of the cavities (right).

SUPERTRIPTYCENE

One can construct 24 iptycenes (excluding enantiomers) by fusing from 0-6 9,10-anthradiyl moieties to the benzenoid bonds of triptycene.[5] We suggested the trivial name 'supertriptycene' for **37**, the ultimate such structure. The synthesis of **37** was completed in 8 steps and 33% overall yield from diene **32**, as shown in Scheme VI[25].

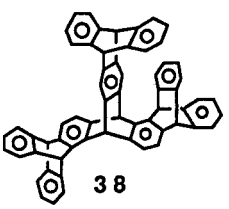
***Scheme VI*[25]**



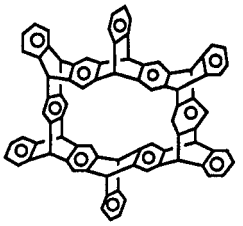
Supertriptycene **37** is a $C_{104}H_{62}$ hydrocarbon with D_{3h} symmetry. It has three large cavities, each lined with six benzenoid rings. It is soluble in hot decalin, tetrachloroethene and benzonitrile. Beautiful crystals can be obtained from a mixture of tetrachloroethene and ethyl acetate, but unfortunately these contain solvent molecules in the cavities, thus destroying the symmetry, and it has not been possible to solve the X-ray structure. The NMR spectra of **37** show seven proton signals and 12 carbon signals as required. Supertriptycene is extremely stable, and does not begin to show a weight loss on thermogravimetric analysis until 580 °C.

OTHER IPTYCENES

Helically chiral iptycenes such as **38** have been synthesized, but cycloiptycenes[5,16] such as **39** remain a synthetic challenge, although some approaches to these attractive synthetic targets have been developed.[17]



38



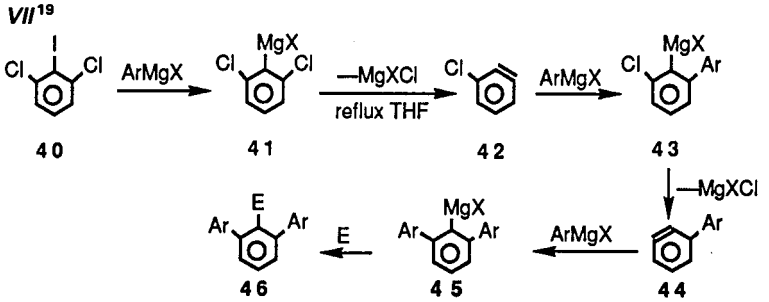
39

REACTION OF POLYHALOARENES WITH GRIGNARD REAGENTS: TANDEM ARYNE REACTIONS

Whereas the iptycene chemistry described in the first part of this paper arose mainly from studying cycloadditions to arynes, the cuppedophane and cappedophane chemistry described in the second half of this paper arose from a study of multiple nucleophilic additions of Grignard reagents to arynes. As aryne precursors, we selected various polyhalobenzenes as analogues of the 1,2-dihalobenzenes used as benzyne precursors.[1] Aryne formation was initiated by metal-halogen exchange, using Grignard reagents rather than the more extensively studied lithium analogues.[18]

An extremely useful *m*-terphenyl synthesis involves *tandem* aryne formation. Treatment of 1,2,3-trihalobenzenes with aryl Grignard reagents provides an excellent one-pot *m*-terphenyl synthesis (Scheme VII).[19] Metal-halogen exchange occurs at the central halogen atom. This step can be carried out separately using vinylmagnesium bromide. The resulting Grignard **41** is stable at -20 to 0° C, but when it is added to a refluxing THF solution of an aryl Grignard the *m*-terphenyl Grignard **46** is produced in good yield. The reaction proceeds via arynes **42** and **44**, nucleophilic addition to which is highly regioselective. The method is excellent for synthesizing *m*-terphenyls **46** with functionality (E) at $C_{2'}$.

Scheme VII[19]



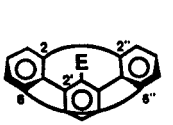
40 **41** **42** **43** **44** **45** **46**

In a like manner, 1,2,4,5-tetrahalobenzenes give *p*-terphenyls,[20] 1,2,3,4,-tetrahalobenzenes give 1,2,3-triarylbenzenes,[21] and hexahalobenzenes give 1,2,4,5-tetraarylbenzenes.[22]

In the next sections the application of these synthesis to the construction of novel aromatic cyclophanes and cappedophanes is described.

CUPPEDOPHANES AND CAPPEDOPHANES FROM *m*-TERPHENYLS

m-Terphenyls with substituents at positions 2,2",6,6" have the 'outer' rings roughly orthogonal to the central ring. Linkage between 2,2" and 6,6" should be facile, to create cuppedophanes **47** and cappedophanes **48**, and as a consequence of the *m*-terphenyl synthesis (Scheme VII), functionality E can be incorporated in the center of the cup (**47**) or cavity (**48**), at $C_{2'}$.

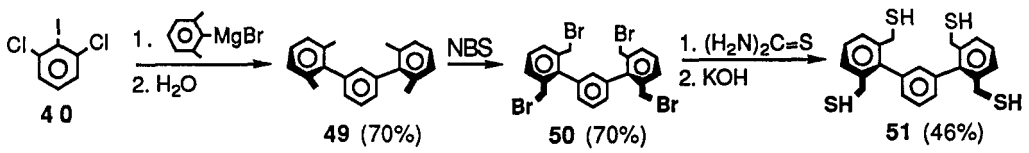


47

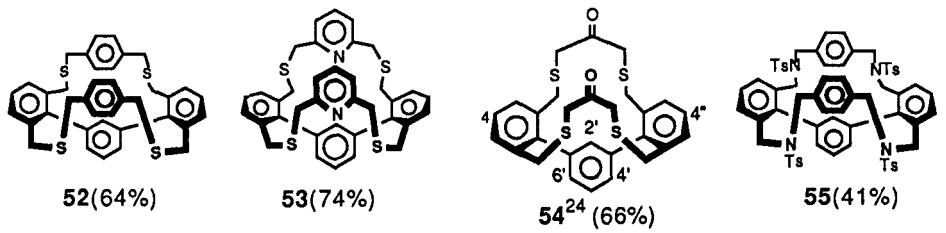
48

The valuable synthetic intermediates **50** and **51** were readily prepared using tandem aryne technology (Scheme VIII).[23]

Scheme VIII[23]

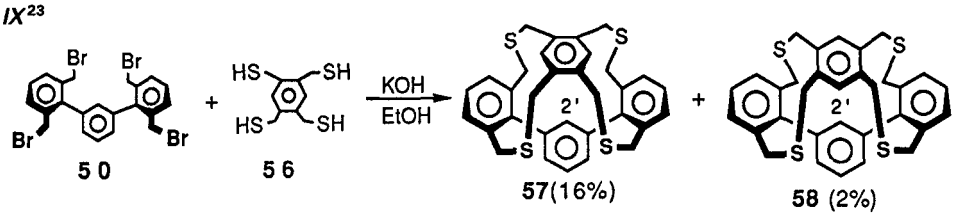


Some examples of cuppedophanes prepared from these intermediates are **52-55.**



Reaction of **50** with tetranucleophile **56** gave the two cappedophanes **57** and **58** (Scheme IX). The ^{1}H NMR spectra readily distinguished the two isomers. The aromatic protons of the capping ring in **57** appeared at δ 4.75, shielded by the 'outer' *m*-terphenyl rings, whereas in **58** these protons appeared at δ 8.30. The internal aryl

Scheme IX[23]



proton at $C_{2'}$ was highly shielded in both isomers (δ 3.97 and 4.23 respectively). Figure 3 shows an X-ray structure of **57**; $H_{2'}$ is only 2.16 Å from the mean plane of the capping ring (which is nonplanar). Even so, it is possible to extrude the four sulfurs from **57**, via oxidation to the tetrasulfone and flash vacuum pyrolysis.[23]

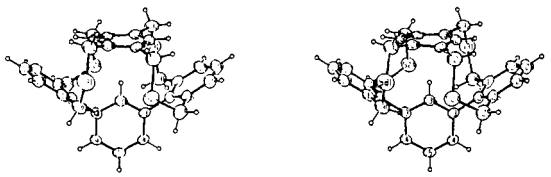
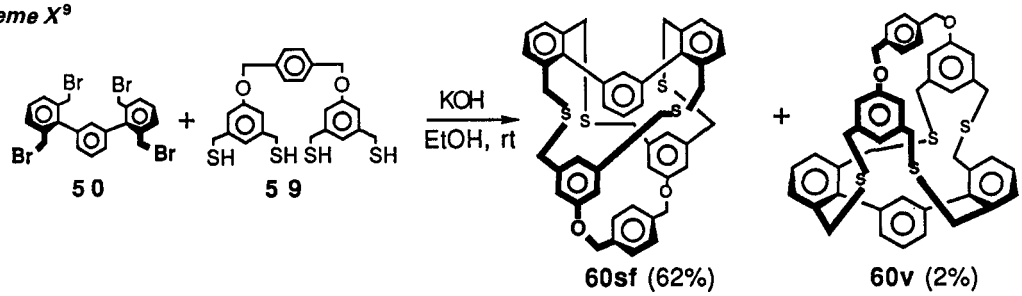


Figure 3. Stereoview of **57** showing nonplanarity of the cap and twisting of the linking arms.

SELF-FILLED AND VAULTED CAPPEDOPHANES

The arms in cappedophanes **57** and **58** are too short to permit the inclusion of any substituent at $C_{2'}$ larger than a proton. To enlarge the cavity, it seemed necessary to lengthen the arms; also, they would have to be stiffened, because flexible links might allow collapsed conformations that would diminish the cavity volume. Consequently tetrathiol **59** was constructed (in place of **56**) for reaction with tetrabromide **50**.[25] To our surprise, the major product was the self-filled conformer **60sf**, with the vaulted conformer **60v** being formed in only small amounts (Scheme X). The two conformers, which are not interconvertible at room temperature, were easily distinguished by their ^{1}H NMR spectra. Thus in **60sf** $H_{5'}$ of the *m*-terphenyl unit appears at δ 4.31 (triplet, J = 7.7 Hz, ortho coupling), highly shielded by the p-xylylene ring; in **60v** $H_{2'}$ is the diagnostic proton (δ 5.70, triplet, J = 1.6 Hz, meta coupling).

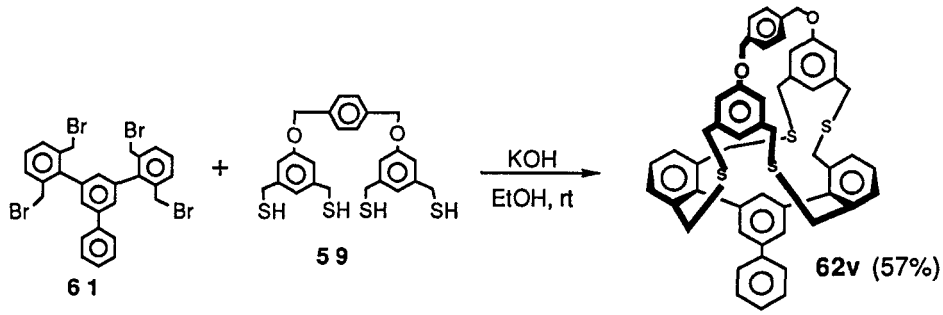
Scheme X[9]



50 **59** **60sf** (62%) **60v** (2%)

The self-filled conformer is thermodynamically more stable than the vaulted conformer, probably because of favorable van der Waals interactions between the central *m*-terphenyl ring and the aryl rings that line the cavity.[26] The energy difference is estimated to be about 3.8 kcal mol.$^{-1}$ This energy difference must be reflected in transition states leading to the two conformers; *i.e.*, approach of **59** from the 'bottom' face of *m*-terphenyl **50** must be preferred. Approach from this face should be hindered by including an appropriately located large group on the central ring of **50**. Indeed, a phenyl group at $C_{5'}$ forced nucleophilic attack from the top face, and gave only vaulted product **62v** (Scheme XI).

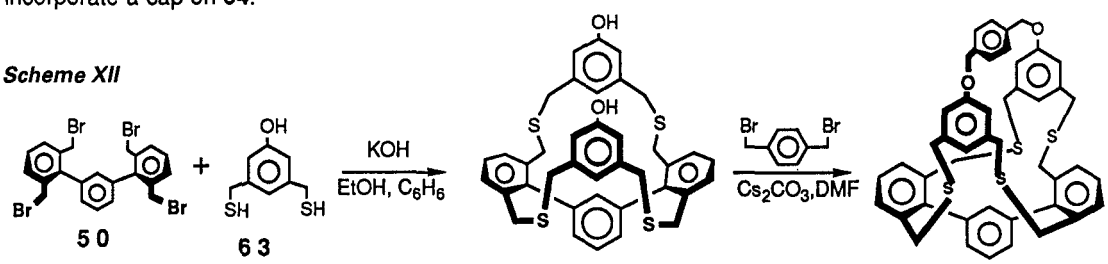
Scheme XI



61 **59** **62v** (57%)

It was also possible to prepare **60v** as the major conformer by first constructing the corresponding cuppedophane, and then adding the cap (Scheme XII). This route is sensitive, however, to the capping group; with *m*- or *o*-xylylene dibromides **64** gave mainly the self-filled conformers. Thus the propensity for forming these conformers is considerable, and the development of a good synthetic route to vaulted cappedophanes with encapsulated functionality remains a challenge. One promising route is to use acylation instead of alkylation to incorporate a cap on **64**.[27]

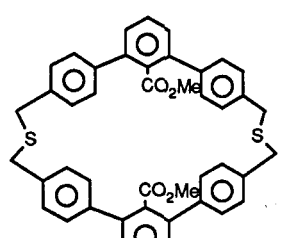
Scheme XII



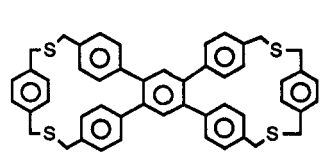
50 **63** **64** **60v** (51%) + trace of **60sf**

OTHER CYCLOPHANES VIA TANDEM ARYNE DERIVED PRECURSORS

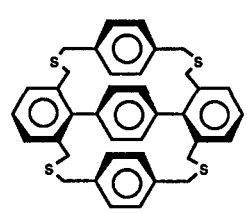
The ready availability of substituted *m*-terphenyls, 1,2,4,5-tetraarylbenzenes and other polyaryl frameworks via tandem aryne sequences prompted us to use these intermediates for the construction of some novel cyclophanes such as **65-67**.



65[28] (50%)



66[29]



67[30]

CONCLUSIONS

The use of diaryne equivalents and multiple or tandem aryne reactions to quickly assemble iptycenes (via cycloaddition reactions) or cappedophanes and other novel cyclophanes (via nucleophilic additions to arynes) has been illustrated. The groundwork is thus laid for the synthesis of useful materials based on this technology.

Acknowledgement

I thank the National Science Foundation (CHE 90-08503) and the National Institutes of Health (GM-15997) for financial support and my students whose names are mentioned in the references for their skill, creativity and friendships.

REFERENCES

1. R. W. Hoffmann, Dehydrobenzene and Cycloalkynes, Academic Press, New York, 1967.
2. H. Hart, C-y. Lai, G. Nwokogu, S. Shamouilian, A. Teuerstein and C. Zlotogorski, J. Am. Chem. Soc. 102, 6649 (1980).
3. H. Hart, C-y. Lai, G. C. Nwokogu and S. Shamouilian, Tetrahedron 43, 5203 (1987).
4. H. Hart, S. Shamouilian and Y. Takehira, J. Org. Chem. 46, 4427 (1987).
5. H. Hart, A. Bashir-Hashemi, J. Luo, and M. A. Meador, Tetrahedron 42, 1641 (1986).
6. Several isolated examples of pentiptycenes had ben described earlier: V. R. Skvarchenko and V. K. Shalaev, Dokl. Akad. Nauk SSSR (Engl. Transl.) 216, 307 (1974); J. I. G. Cadogan, M. J. P. Harger and J. T. Sharp, J. Chem. Soc. B 602 (1971); E. Clar. Chem. Ber. 64, 1676 (1931); W. Theilacker, U. Berger-Brose and K. H. Beyer, ibid. 93, 1758 (1960); P. Yates and P. Eaton, J. Am. Chem. Soc. 82, 4436 (1960).
7. H. Hart, N. Raju, M. A. Meador and D. L. Ward, J. Org. Chem. 48, 4357 (1983).
8. A. Bashir-Hashemi, H. Hart and D. L. Ward, J. Am. Chem. Soc. 108, 6675 (1986).
9. Y.-S. Chen and H. Hart, J. Org. Chem. 54, 2612 (1989).
10. K. Shahlai and H. Hart, J. Am. Chem. Soc. 110, 7136 (1988).
11. C. F. Huebner, R. T. Puckett, M. Brezchfta and S. L. Schwartz, Tetrahedron Lett. 359 (1970).
12. K. Shahlai and H. Hart, J. Org. Chem. 54, 2615 (1989).
13. K. Shahlai and H. Hart, J. Am. Chem. Soc. 112, 3687 (1990); K. Shahlai and H. Hart, J. Org. Chem. 56, 6905 (1991).
14. S. B. Singh and H. Hart, J. Org. Chem. 55, 3412 (1990).
15. K. Shahlai, H. Hart and A. Bashir-Hashemi, J. Org. Chem. 56, 6912 (1991).
16. H. R. Karfunkel and T. Dressler, J. Am. Chem. Soc., 114, 2285 (1992).
17. Unpublished results with K. Shahlai.
18. Organolithium reagents are considerably more basic than the analogous Grignard reagents. Since halogen substitution increases the acidity of aryl protons, lithium reagents react with polyhalobenzenes in two ways, by metal-halogen exchange and by proton removal. Grignard reagents, on the other hand, react mainly by metal-halogen exchange. Consequently, in all the reactions described here regiochemistry can be better controlled and yields are much higher with Grignard vis-a-vis the corresponding lithium reagents.
19. C-J. F. Du, H. Hart and K-K. D. Ng, J. Org. Chem. 51, 3162 (1986).
20. H. Hart and K. Harada, Tetrahedron Lett. 26, 29 (1985); H. Hart, K. Harada and C-J. F. Du, J. Org. Chem. 50, 3104 (1985).
21. T. Ghosh and H. Hart, J. Org. Chem. 53, 3555 (1988).
22. K. Harada, H. Hart and C-J. F. Du, J. Org. Chem. 50, 5524 (1985).
23. T. K. Vinod and H. Hart, J. Am. Chem. Soc., 110, 6574 (1988); T. K. Vinod and H. Hart, J. Org. Chem. 55, 881 (1990).
24. Unpublished results with J-J. Chiu and R. S. Grewal.
25. T. K. Vinod and H. Hart, J. Am. Chem. Soc. 112, 3250 (1990); T. K. Vinod and H. Hart, J. Org. Chem. 56, 5630 (1991).
26. For another example of this phenomenon see Y. Rubin, K. Dick, F. Diederich and T. M. Georgiadis, J. Org. Chem. 51, 3270 (1986) and R. J. Loncharich, E. Seward, S. B. Ferguson, F. K. Brown, F. Diederich and K. N. Houk, J. Org. Chem. 53, 3479 (1988).
27. Unpublished results with T. K. Vinod.
28. Unpublished results with P. Rajakumar.
29. Unpublished results with S. O. Acquaah.
30. Unpublished results with Jer-Jye Chiu.