

New interesting molecular topologies by way of modern cross-coupling reactions*

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Abstract: Modern transition-metal-catalyzed cross-coupling reactions, especially of the Kumada, Heck, and Suzuki types, have provided facile access to various bridge-annelated [2.2]paracyclophane derivatives including trifoliaphane and its tribenzo analog. The reduction of trifoliaphane with potassium metal in [D₈]-THF led to hexakis[*p*-benzyl]benzene anion, which could efficiently be trapped with various electrophiles. Highly efficient multi-fold Suzuki couplings were performed with hexabromobenzene, octabromonaphthalene, and hexabromotriphenylene. The obtained hexa- and octaalkenylarene derivatives disclose interesting molecular shapes. Eventually, a newly developed cascade coupling of bromoarenes containing *peri*-positioned C–H bonds has led to indeno-annelated polycyclic aromatic hydrocarbons including indenocorannulene as well as the tetrakis- and tris(*tert*-butylindeno)pyrene which disclose very interesting spectroscopic properties. In particular, tetrakis(*tert*-butylindeno)pyrene self-assembles in solution by way of π -stacking, and it can be reduced with potassium metal to a stable dianion, a readily dimerizing trianion radical, and a tetraanion.

Keywords: [2.2]paracyclophanes; palladium catalysis; cross-couplings; hexaalkenylbenzenes; carbanions.

INTRODUCTION

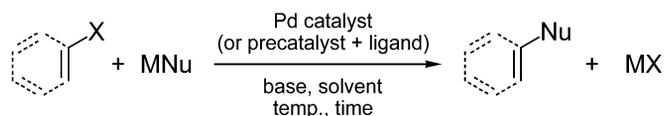
As has been evident throughout this conference, transition-metal-catalyzed cross-coupling reactions have become an essential tool for the assembly of functional π -systems of all sorts. Nobody has to be persuaded any more that the application of these tools frequently offers the most efficient way to approach certain target molecules. Yet, there is ongoing active development, as has been reviewed in two

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recent comprehensive books [1,2]. In our efforts to assemble new interesting molecular 6π -electron topologies, we have predominantly applied palladium-catalyzed cross-coupling reactions of Grignard reagents (Kochi variant of the original Kumada coupling), boronic acid derivatives (Suzuki coupling), and alkenes (Mizoroki–Heck coupling) to alkenyl and aryl halides (Scheme 1).



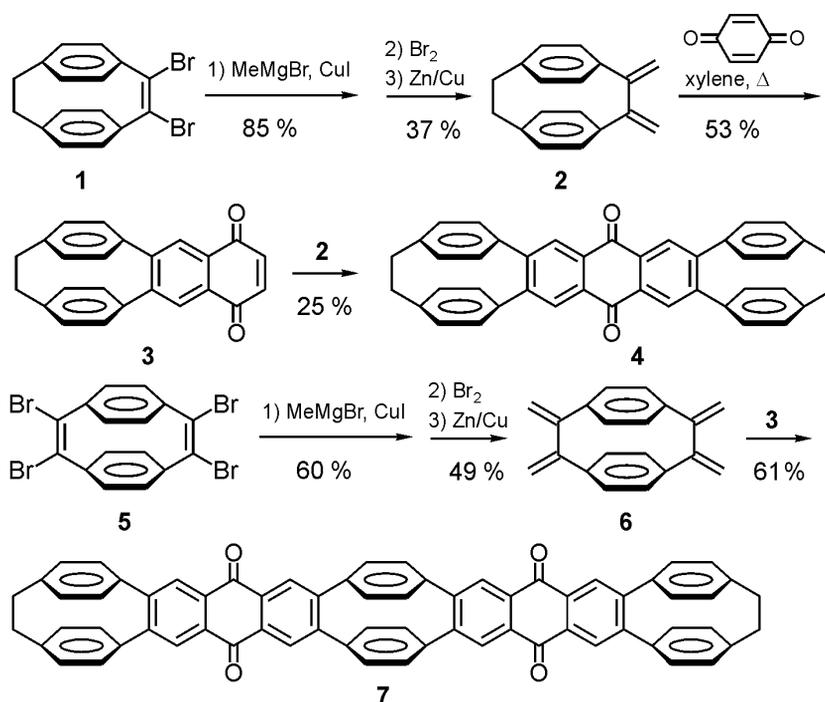
Alkenyl or Aryl with X = I, Br, Cl, OTf, ONf, N_2^+ , PhI^+ , $OP(OR)_2$

MNu	Name	MNu	Name
BrMgR	(Kumada), Kochi	Cu—≡—R	Stevens-Castro, Sonogashira
B(OR') ₂ R	Suzuki	H ₂ C(EWG) ₂	Yamamoto
ClZnR	Negishi, Knochel	HNR ₂	Buchwald, Hartwig
XAIR ₂	Negishi	HOR	Buchwald, Hartwig
XSiR' ₂ R	Hiyama, Denmark	H ₃ COAr	Buchwald, Hartwig
H—C=C—R	Heck, (Mizoroki)		

Scheme 1 Pd-catalyzed cross-coupling reactions [1,2].

RESULTS AND DISCUSSION

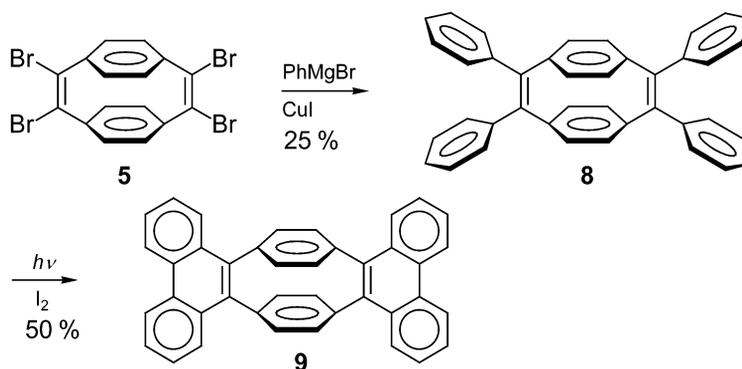
We first applied metal-catalyzed cross-coupling reactions almost 20 years ago in a project to extend the [2.2]paracyclophane skeleton by ring annelations onto the two-carbon bridges in a more general way than Wong et al. had demonstrated with the first synthesis of dibenzo[2.2]paracyclophane [3]. This endeavor aimed at an extension of the [2.2]paracyclophane skeleton in the third dimension, which had not been considered in preceding extensions by Misumi [4] and Hopf [5]. The twofold coupling of methylmagnesium bromide under copper(I) iodide catalysis with 7,8-dibromo[2.2]paracyclophane-7-ene (**1**) gave the corresponding dimethyl-substituted compound from which, by bromination and debromination, 7,8-dimethylene[2.2]paracyclophane (**2**) was obtained. Along an analogous route, the tetrabromoparacyclophanediene **5** via the tetramethyl compound gave the tetramethylene[2.2]paracyclophane **6** (Scheme 2) [6]. Both the diene **2** and the bisdiene **6** can be applied in Diels–Alder reactions, e.g., with *para*-benzoquinone (Scheme 2).



Scheme 2 Bridge-extended [2.2]paracyclophanes [6].

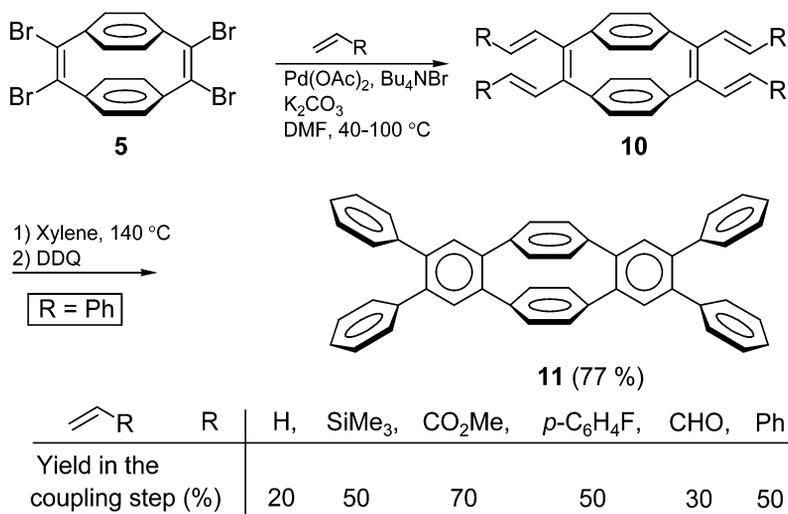
Thus, twofold [4+2] cycloaddition of the diene **2** to benzoquinone gave the bis[2.2]paracyclophane **4** linked by an anthraquinone unit, while twofold addition of the 1:1 adduct **3** of the diene **2** and benzoquinone onto the bisdiene **6** gave the molecule **7** consisting of three [2.2]paracyclophane moieties linked by two anthraquinone units [6]. These molecules and others prepared by us can be conceived as electron-storage systems with several separately addressable storage boxes [7].

The analogous coupling of tetrabromo[2.2]paracyclophane diene **5** with phenylmagnesium bromide gave 7,8,15,16-tetraphenyl[2.2]paracyclophane-7,15-diene (**8**) which, upon irradiation in the presence of iodine, gave the bisphenanthrene-annellated [2.2]paracyclophane diene **9** (Scheme 3) [6].



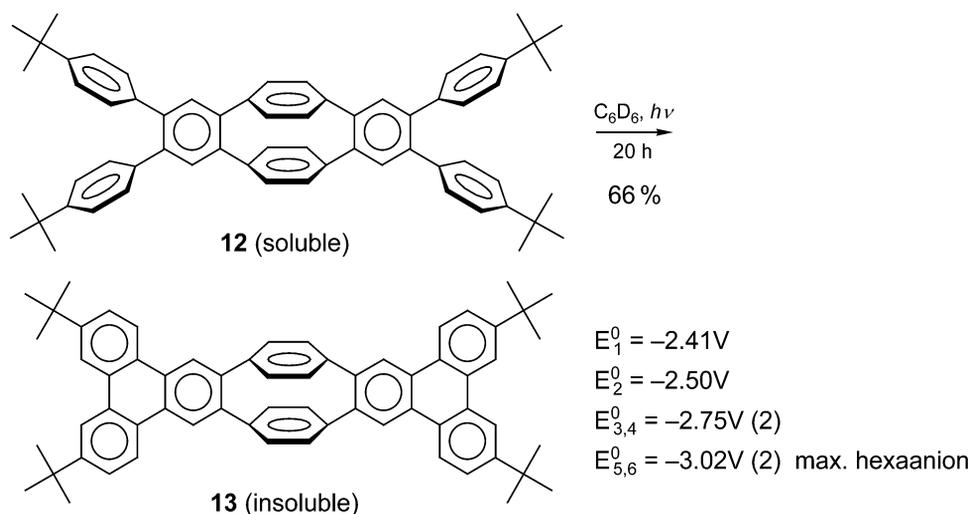
Scheme 3 A rapid access to bisphenanthrene-annellated [2.2]paracyclophane diene [6].

The most general route to arene-annulated [2.2]paracyclophanedienes, however, started with the fourfold Heck coupling of an alkene to tetrabromo[2.2]paracyclophanediene **5**, first synthesized in our laboratory (Scheme 4) [8]. This readily leads to the [2.2]paracyclophanedienes **10** with 1,3,5-hexatrienes attached to the bridges, and these, as they are (*E,Z,E*)-configured, readily undergo 6π -electrocyclization and subsequent dehydrogenation to give the corresponding 7,8,14,15-bisbenzene-annulated [2.2]paracyclophanediene **11** [9].



Scheme 4 A facile access to bridge-annulated areno[2.2]paracyclophanedienes [8].

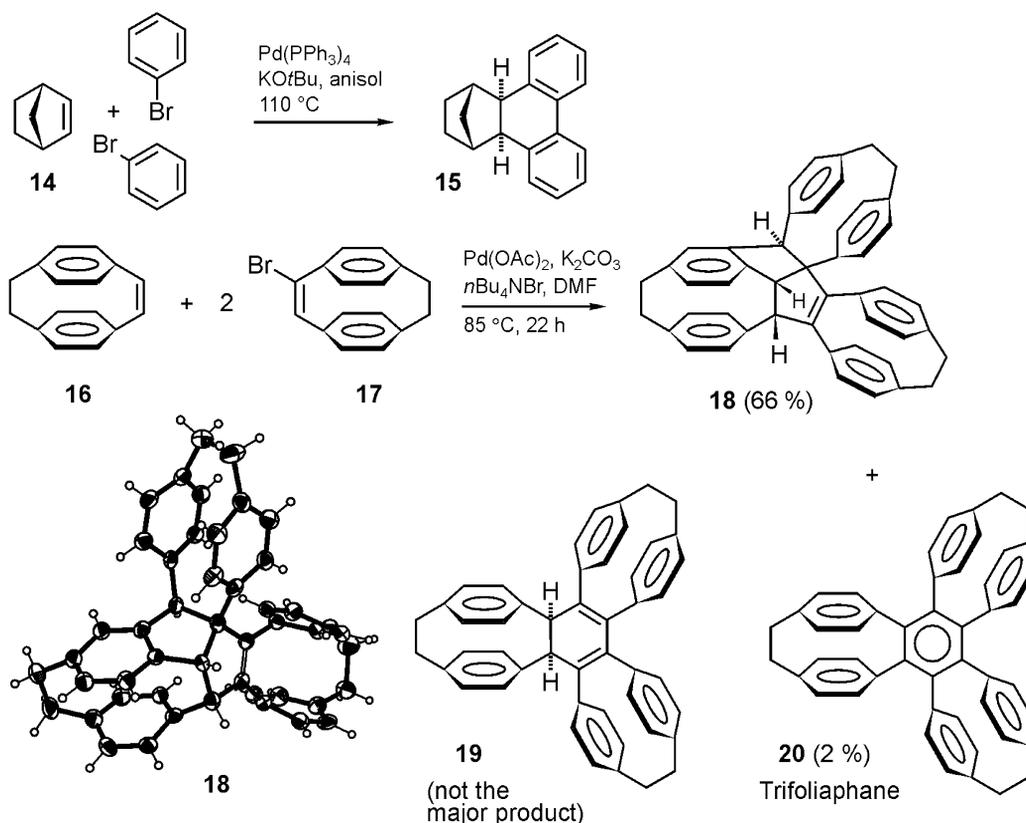
Such compounds with additional four aryl substituents can be photocyclized to triphenylene-annulated [2.2]paracyclophanedienes, as was demonstrated for the *tert*-butyl-substituted compound **12** (Scheme 5). Although the *tert*-butyl groups made the starting material soluble in benzene, the cyclization product **13** precipitated from the solution upon irradiation of **12**.



Scheme 5 Preparation of a twofold triphenylene-annulated [2.2]paracyclophanediene [9].

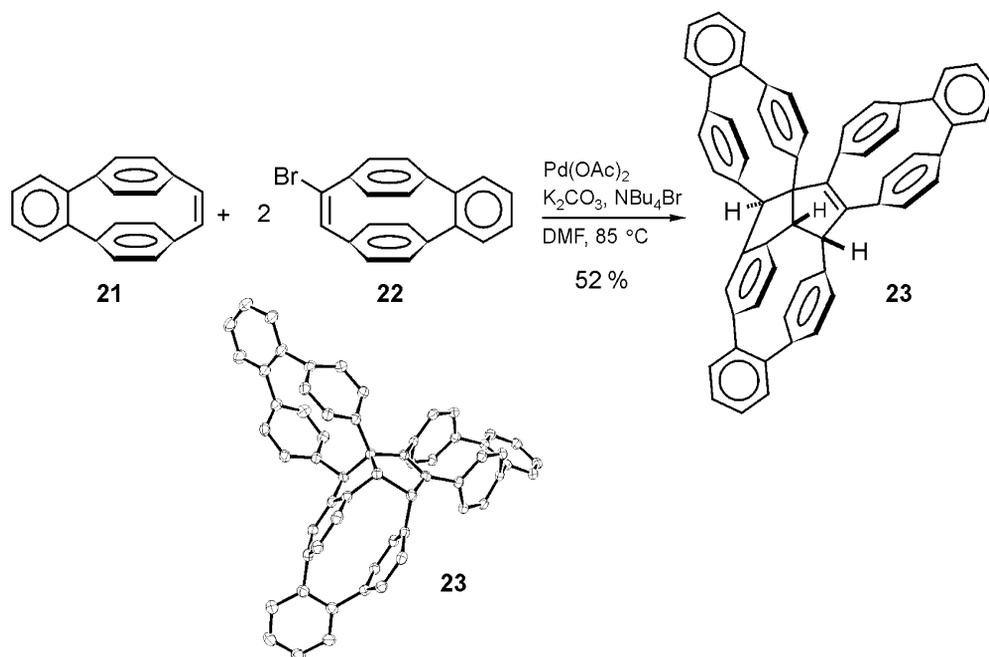
However, the hydrocarbon and the anions generated from it were soluble in tetrahydrofuran and were fully characterized by NMR spectroscopy. The compound **13** could be charged up to a hexaanion, i.e., it accommodated a total of up to six electrons in two single and two double electron transfer stages [9].

In trying to adopt a known palladium-catalyzed [2+2+2] assembly of norbornene (**14**) with two bromobenzene units (Scheme 6) [10] to yield the norbornane-annulated dihydrophenanthrene **15**, [2.2]paracyclophan-7-ene (**16**) was treated with 2 equiv of 7-bromo[2.2]paracyclophan-7-ene (**17**) under Jeffery conditions for Heck couplings.



Scheme 6 One known Pd-catalyzed [2+2+2] assembly of a dibenzo-annulated cyclohexadiene [10] and an unexpected new domino-coupling process [11].

Under these conditions, the predominant reaction proceeded in a completely different way, yielding the polycyclic hydrocarbon **18** in which all three starting molecules had been incorporated, but the central ring system is a bicyclo[3.3.0]octene, apparently formed by incorporation of one of the *ortho*-positions of one benzene deck in one of the three [2.2]paracyclophane moieties. The threefold [2.2]paracyclophane-annulated benzene, first synthesized by Hopf et al. and termed “trifoliaphane” [12], apparently stemming from the originally expected [2+2+2] cocyclization product **19**, was indeed isolated as a minor component in 2 % yield. The structure of the unexpected polycycle **18** was rigorously proved by an X-ray structure analysis, and so was the structure of a completely analogous product obtained from 14,15-benzo[2.2]paracyclophane-7-ene (**21**) and 2 equiv of its monobromo derivative **22** under palladium catalysis (Scheme 7) [11].

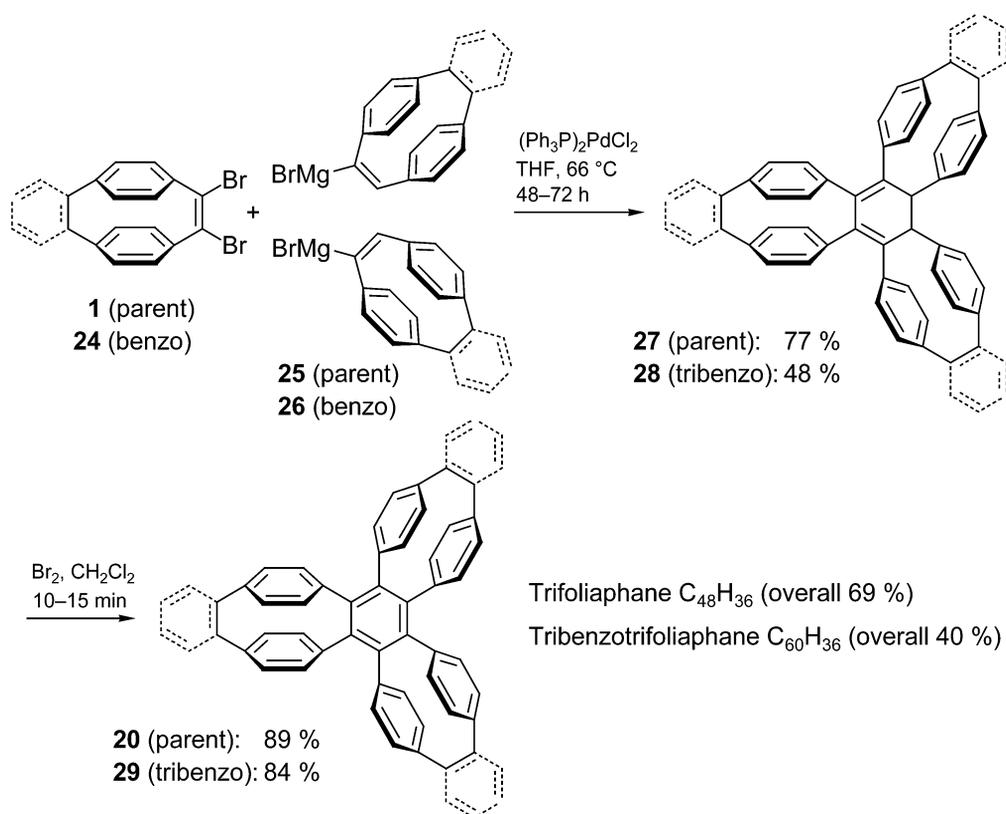


Scheme 7 Facile assembly of a $\text{C}_{60}\text{H}_{38}$ hydrocarbon [11].

This constitutes a rather facile assembly of a polycyclic $\text{C}_{60}\text{H}_{38}$ hydrocarbon, yet high-temperature pyrolysis of this skeleton did not provide any C_{60} -fullerene.

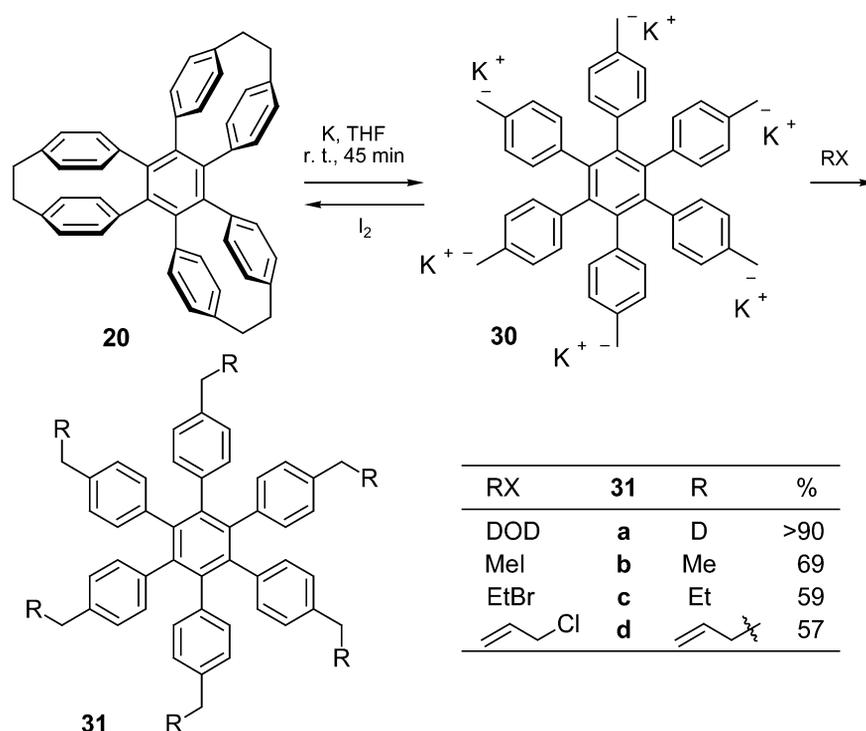
Eventually, highly productive syntheses of trifoliaphane **20** and tribenzotrifoliaphane **29** were accomplished by a twofold palladium-catalyzed coupling of the Grignard reagent **25** prepared from [2.2]paracyclophan-7-ene onto 7,8-dibromo[2.2]paracyclophan-7-ene (**1**), adopting a protocol of Kochi et al. [13]. This twofold cross-coupling reaction, which initially must yield a tris[2.2]paracyclophan-7-ene-annulated 1,3,5-hexatriene, proceeded directly to the 6π -electrocyclization product **27** in 77 % yield [14]. Treatment of the latter with bromine in methylene chloride gave the trifoliaphane **20** with a central aromatic core in an overall yield of 69 % [14].

By complete analogy, the tribenzotrifoliaphane **29**, a $\text{C}_{60}\text{H}_{36}$ hydrocarbon, was obtained in 40 % overall yield along the same route from the Grignard reagent of 7-bromo-15,16-benzo[2.2]paracyclophanediene **26** and 7,8-dibromo-15,16-benzo[2.2]paracyclophanediene (**24**) (Scheme 8).



Scheme 8 Highly productive syntheses of trifoliaphane and tribenzotrifoliaphane [14].

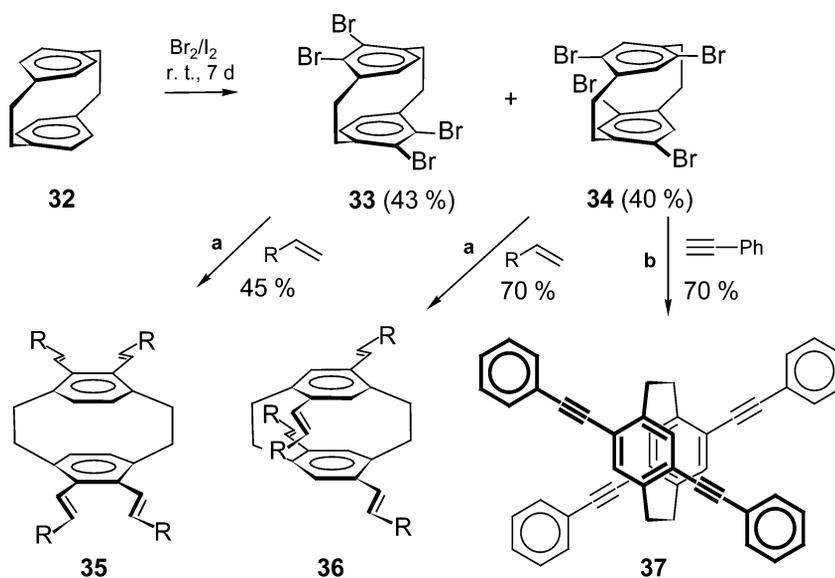
Both trifoliaphane **20** and tribenzotrifoliaphane **29** were fully characterized by X-ray structure analyses, and their multiple charging was investigated. While none of the charged species derived from the tribenzo derivative **29** could be identified, stepwise multiple charging of the parent trifoliaphane **20** with potassium in tetrahydrofuran at room temperature proceeded cleanly and gave a hexaanion, which turned out to be the hexakis(*p*-tolyl)benzene hexaanion **30**. It apparently was formed by cleavage of all three saturated bridges in the starting material. Facile cleavage of two-carbon bridges in the parent [2.2]paracyclophane upon reduction to the radical anion is well known [15]. Thus, this behavior of trifoliaphane was not surprising, however, the cleanliness of this process is remarkable, as the hexaanion **30** can be completely recycled to the trifoliaphane **20** by treatment with iodine, and it can also be trapped with a variety of electrophiles. Accordingly, trapping with deuterium oxide gave the hexa-deuteriohexakis-*p*-tolylbenzene **31a** in virtually quantitative yield. Other sixfold substitution products, such as the hexakisethyl **31b**, hexakispropyl **31c** and hexakisbutenyl derivative **31d** could also be isolated in good yields (57–69 %). While the preparation of hexasubstituted benzene derivatives is quite facile by metal-mediated trimerization of appropriately substituted acetylenes [16], this new access to such compounds may complement other approaches, as novel substitution patterns may be realized (Scheme 9) [14].



Scheme 9 Trifoliaphane—a rigid all-orthogonal hexaphenylbenzene derivative and its sixfold reduction [14].

Multiple couplings of the Heck and Sonogashira type were also applied to the two isomeric tetrabromo[2.2]paracyclophane derivatives **33** and **34**, which can best be prepared by leaving [2.2]paracyclophane (**32**) in liquid bromine in the presence of traces of iodine for seven days at room temperature (Scheme 10) [17]. The two isomeric tetrabromides, which had previously been described by Cram et al. [18], when prepared along this route, can easily be separated by crystallization. Their fourfold Heck coupling with methyl acrylate, styrene, and *para*-methoxystyrene as well as Sonogashira coupling with phenylacetylene all gave interesting skeletons **35–37**, which offer themselves for studies of intramolecular charge-transfer phenomena [19].

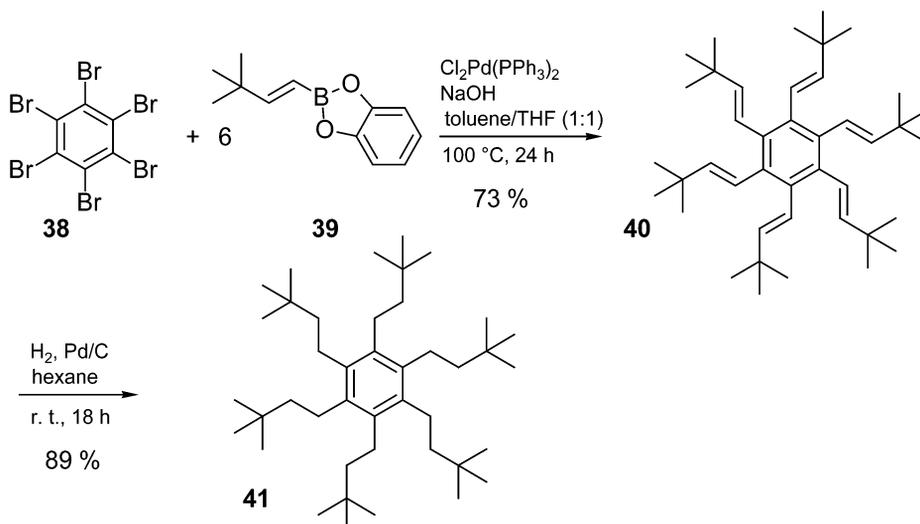
For such multiple Heck couplings, the modified conditions as developed by Jeffery [20] turned out to be essential. Under such conditions, the twofold coupling of *ortho*-dibromobenzene with methyl acrylate at 100 °C within three days gave the coupling product in 78 % isolated yield, and the same coupling with styrene occurred in 92 % yield at 100 °C in five days [21], while an original report by Heck et al. [22] stated a yield of 37 % for the twofold coupling product from *ortho*-diiodobenzene and styrene. Accordingly, three-, four-, five-, and even sixfold couplings of various styrene derivatives and methyl acrylate on tri-, tetra-, penta-, and hexabromobenzene derivatives were tested. All of them gave the multifold coupling products in yields ranging from 49 to over 70 % [23], however, the sixfold coupling product turned out to be an inseparable mixture of a large variety of isomeric products formed by intramolecular carbopalladation at the intermediate *ortho*-styryl-substituted phenylethylpalladium bromides [24].



a: Pd(OAc)₂, NBu₄Br, K₂CO₃, DMF; R = CO₂Me, C₆H₅, 4-MeOC₆H₄. – b: Pd(PPh₃)₄, CuI, NEt₃.

Scheme 10 New double-layered 1,4-distyryl- and 1,4-di(phenylethynyl)benzene chromophores [17].

Since the hexaalkenylbenzene derivatives were particularly intriguing to us, we sought to approach them by sixfold Suzuki coupling, since by its mechanism such a cross-coupling should not encounter such problems. Incidentally, the very first sixfold Suzuki coupling of hexabromobenzene was tested with the alkenylboronate **39** obtained by hydroboration of *tert*-butylacetylene with catecholborane, and this coupling under typical conditions gave the hexakis(*tert*-butylethenyl)benzene (**40**) in 73 % yield (Scheme 11) [25,26].



Scheme 11 A highly successful sixfold Suzuki coupling [25,26].

Subsequent attempts to perform this sixfold coupling with other alkenylboronates were mostly unsuccessful. Even the hexastyrylbenzene (**42**), which had been prepared by another route in the meantime [27], could not be obtained by sixfold Suzuki coupling of phenylethenylboronate.

The particular success with the (*tert*-butylethenyl)boronate may arise from a favorable preorganization of the already attached substituents with the incoming substituent being delivered by the attached ethenylpalladium substituent due to attractive van der Waals forces. Such attractive van der Waals forces must also play a role in giving the hexakis(*tert*-butylethenyl)benzene (**40**) its bowl shape in the crystal (see Fig. 1).

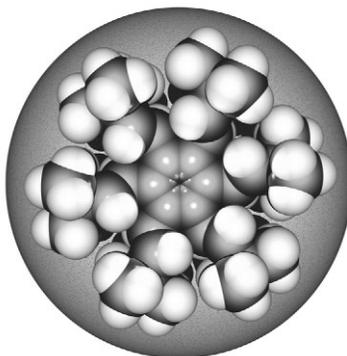


Fig. 1 Structure of hexakis(*tert*-butylethenyl)benzene in the crystal [25].

The six *tert*-butylethenyl arms of the molecule are all pointing toward one side out of the plane of the central ring. However, intramolecular van der Waals attractive forces cannot be the only reason for this preferred conformation, as the parent hexavinylbenzene exists in a similar shape in the crystal [28]. The arrangement of these six side arms in **40** cannot be all that rigid, as catalytic hydrogenation at ambient temperature and pressure cleanly proceeds all the way to the hexakis(*tert*-butylethyl)-substituted derivative **41** (Scheme 11). This fact and the observation that compound **41** in the crystal adopts a conformation, in which the six arms alternatingly point up and down with respect to the central benzene ring. In this case, the molecular shape apparently is dictated by crystal packing effects, as *tert*-butyl groups of two adjacent molecules in the molecular stacks apparently have intermolecular attractive van der Waals interactions [26].

The packing of the hexakis(*tert*-butylethenyl)benzene molecules **40** in the crystal is in layers rather than in stacks, and close intermolecular contacts occur between *tert*-butyl groups within the layers (Fig. 2) [26].

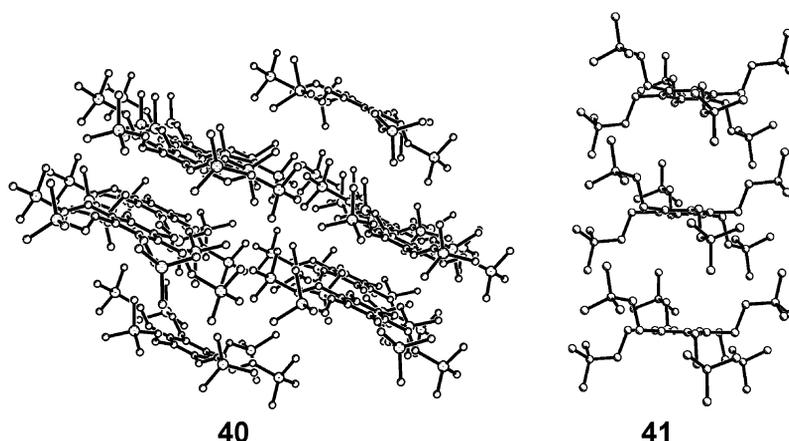


Fig. 2 Crystal packing of hexakis(*tert*-butylethenyl)benzene (**40**) and hexakis(3,3-dimethyl-1-butyl)benzene (**41**).

The steric bulk of the *tert*-butyl groups in the ethenylboronate **39** must play an important role for the success of the sixfold coupling, since an ethenylboronate with any other group mimicking the *tert*-butyl group, like a 1-methylcyclohexyl or a 1-methylcyclopropyl moiety, the sixfold Suzuki coupling products **43** and **44** were obtained in 44 and 16 % yield, respectively (Fig. 3). With a trimethylsilyl group attached, the ethenylboronate could not be coupled, but the corresponding (trimethylsilylethenyl)tributylstannane furnished the sixfold Stille coupling product **45** in 41 % yield [25,26]. For this sixfold Stille coupling, the palladacycle prepared from tris(*o*-tolyl)phosphine and palladium acetate according to Herrmann and Beller [29], turned out to be best.

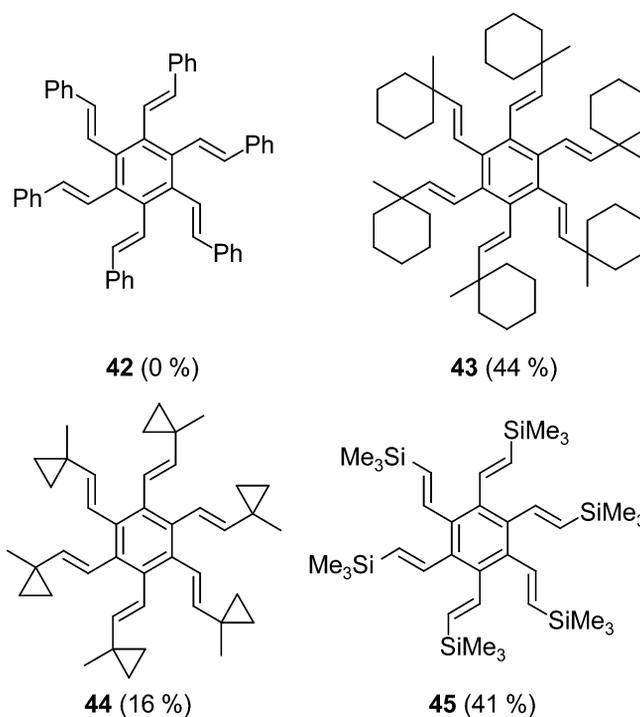


Fig. 3 Some new hexakisalkenylbenzene derivatives by sixfold cross-couplings [26].

Upon standing in sunlight or upon UV irradiation, hexakis(*tert*-butylethenyl)benzene (**40**) turns yellow, and this manifests itself by the occurrence of an additional absorption band in the visible region at 445 nm with a simultaneous decrease in the intensity of the major band at 260 nm (Fig. 4). To a certain extent, this color change is reversible, but the major band does not reach the original intensity, even after 24 h in darkness. A similar phenomenon has been observed for hexavinylbenzene itself [30], but a convincing explanation for this current phenomenon has not yet been found.

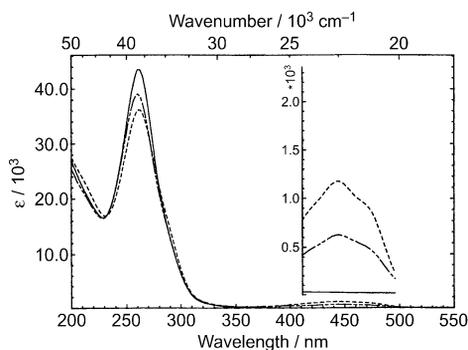
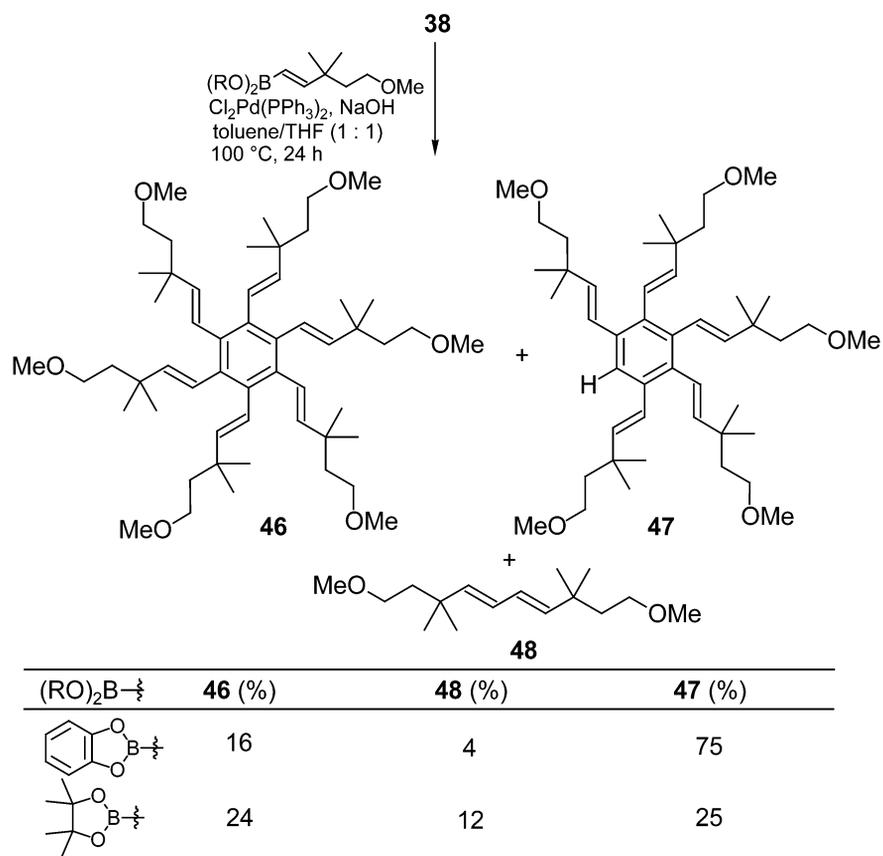


Fig. 4 UV-vis absorption spectra of hexakis(*tert*-butylethenyl)benzene (**40**).

Because of their bowl shape, molecules of type **40** appeared to be potential new motifs for host molecules in supramolecular complexes. Especially with additional polar functionality in the side arms, such molecules might accept appropriate guest molecules. At least one such functionally substituted hexakis(*tert*-alkylethenyl)benzene derivative **46** could be obtained by sixfold Suzuki coupling of the corresponding functionally substituted ethenylboronate, albeit in poor yield (at best 24 %), the byproducts were the fivefold coupling product **47**, in which one of the six bromines had been reductively removed, along with the homo-coupling product **48** of the alkenylboronate (Scheme 12) [26].



Scheme 12 A functionally substituted hexakis(*tert*-alkylethenyl)benzene by sixfold Suzuki coupling [26].

An X-ray structure analysis revealed that the six arms on the central benzene ring in compound **46** in the crystal point alternately up and down with respect to the central ring (Fig. 5). This does not preclude that this compound might act as a proper host for certain guest molecules, however, appropriate cocrystallizations have not yet been carried out.

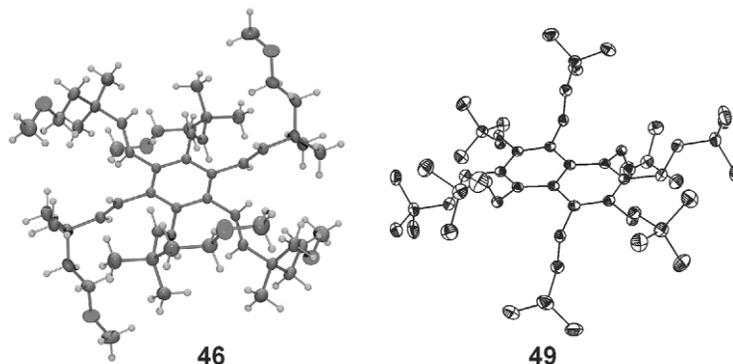
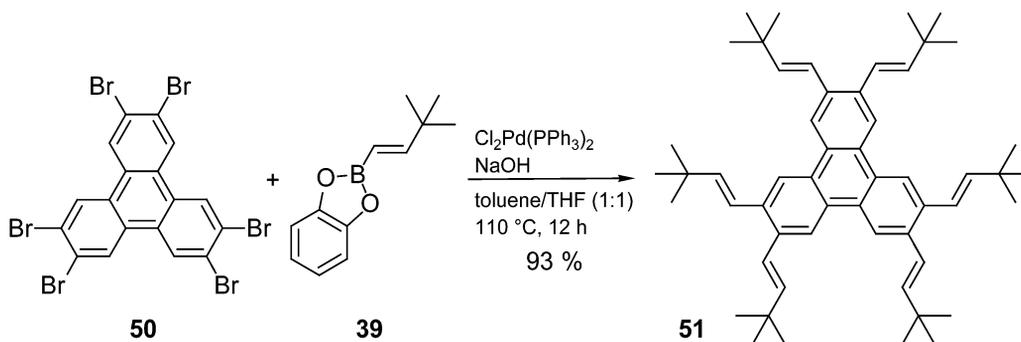


Fig. 5 Structures of hexakis(5'-methoxy-3,3-dimethyl-1-pentenyl)benzene (**46**) and octakis(*tert*-butylethenyl)naphthalene (**49**) in the crystals [26].

The world record in multiple coupling reactions so far has been achieved with octabromonaphthalene which, under similar conditions as hexabromobenzene (**38**) (90 instead of 100 °C, 24 h) with the boronate **39** furnished the eightfold coupling product **49** in 21 % yield. As an X-ray structure analysis disclosed (Fig. 5), the four arms in 1,4,6,7-positions point down, while the other four in 2,3,5,8-positions point up with respect to the naphthalene core. This arrangement, which is different from the ones seen before for hexasubstituted benzene derivatives, is definitely caused by the close proximity of two substituents in the *peri*-positions.

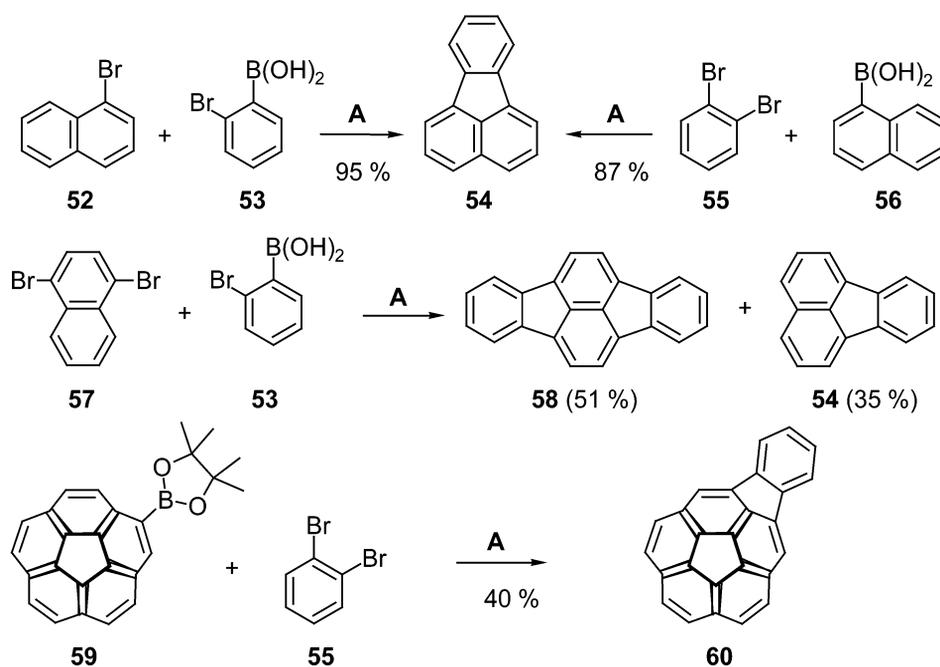
In terms of yield, the record in any multiple cross-coupling reaction certainly came with the six-fold coupling of hexabromotriphenylene **50** which, upon Suzuki coupling with (*tert*-butylethenyl)boronate (**39**), gave the product **51** in 93 % yield. This corresponds to a yield of close to 99 % per newly formed carbon–carbon bond (Scheme 13) [26].



Scheme 13 Sixfold Suzuki coupling with hexabromotriphenylene.

With respect to efficiency, the cascade coupling of an *ortho*-bromobenzenboronic acid (**53**) with 1-bromonaphthalene (**52**) and 1,4-dibromonaphthalene (**57**) leading to the indeno-annelated products **54** and **58**, respectively, are quite remarkable as well (Scheme 14).

The same indeno-annulation can be achieved with *ortho*-dibromobenzene (**55**) and a boronic acid or boronate of an aromatic system with a free *peri*-position such as naphthalene-1-boronic acid (**56**) as well as the corannuleneboronate **59**. While the latter furnishes the indeno-annelated corannulene in only 40 % yield, the fluoranthene (**54**) is obtained in 87 % yield (Scheme 14) [29]. It would be desirable to have the C_5 -symmetrical pentabromocorannulene available and perform this cascade coupling five times with *ortho*-bromobenzenboronic acid (**53**) to obtain the highly curved pentaindenocorannulene, a $C_{50}H_{20}$ hydrocarbon. Unfortunately, the known pentachlorocorannulene could not successfully be coupled in this manner under the conditions applied so far.



A: Pd₂(dba)₃ (20 %), P(Cy)₃, DBU, DMF, 155 °C, 48 h.

Scheme 14 A new cascade coupling for indeno[1,2,3]-annulations of polycyclic aromatic hydrocarbons [31].

The indeno-annulation motif is also present in tetraindenopyrene, which is part of the belt of C₇₀-fullerene (Fig. 6).

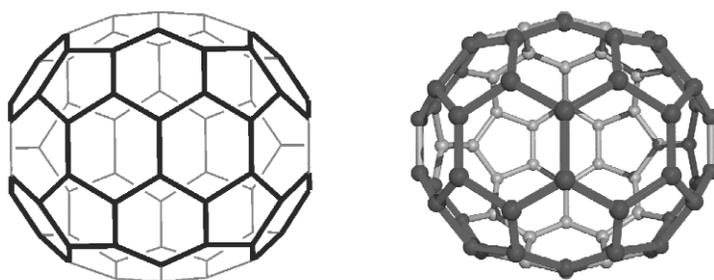
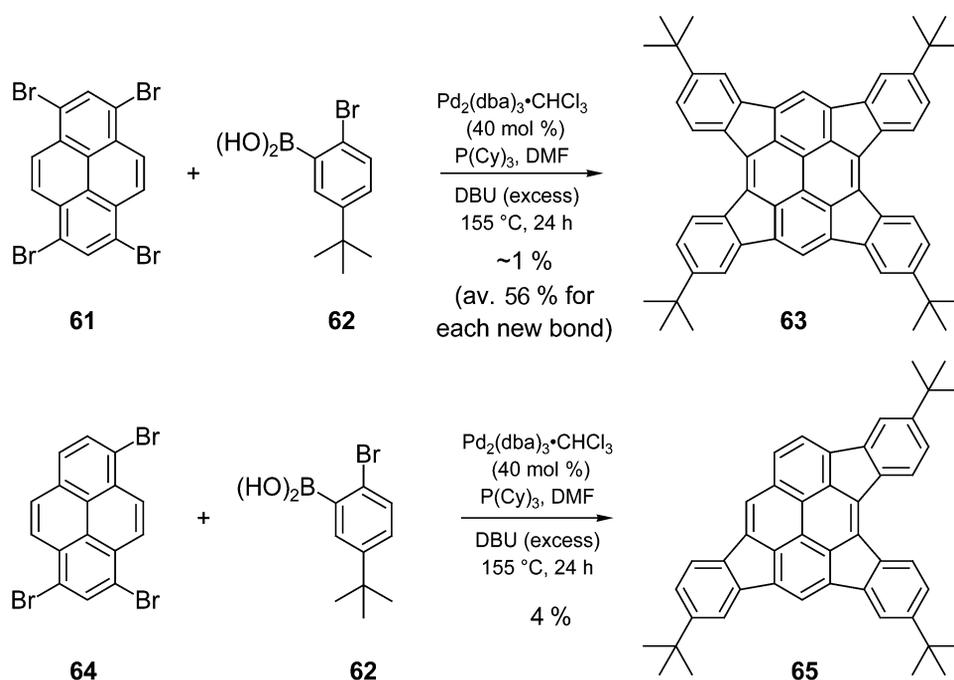


Fig. 6 Tetraindenopyrene mapped onto C₇₀-fullerene.

Since tetrabromopyrene **61** is readily available from pyrene by bromination [32], it was coupled with *ortho*-bromobenzenboronic acid (**53**) under the conditions stated above, but the material obtained was completely insoluble. To improve solubility, this cascade coupling was subsequently performed with 4-*tert*-butyl-2-bromobenzenboronic acid (**62**), employed with 20 % excess, to furnish the tetrakis(*tert*-butylindeno)pyrene **63**. The crude yield obtained was on the order of 5 %, but repeated column chromatography was essential to obtain the material in pure form, and thus the isolated yield dropped to about 1 % (corresponding to an average of 56 % for each new bond) (Scheme 15) [33].

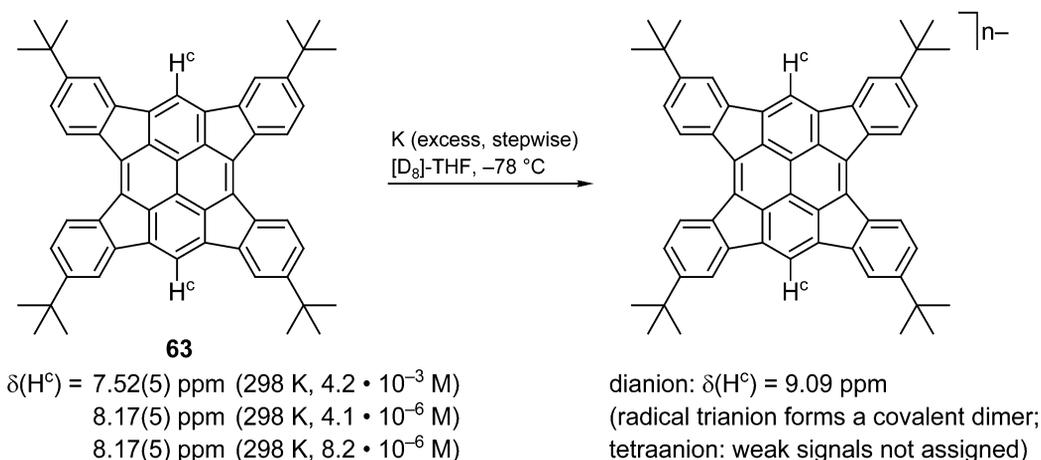


Scheme 15 Tetraindenopyrene- and triindenopyrene from 1,3,6,8-tetrabromo- and 1,3,6-tribromopyrene [33].

The analogous coupling of 1,3,6-tribromopyrene (**64**) with **62** gave the triindenopyrene **65** in 4% yield. The new indenopyrenes **63** and **65** show interesting UV-vis and fluorescence spectra. The tetraindenopyrene derivative **63** has a longest wavelength absorption at 550 nm with a shoulder at 590 nm. The longest wavelength absorption of **65** appears at 515 nm. Thus, the nonalternate polycyclic aromatic hydrocarbon **63** is deep red. The ^1H NMR spectrum discloses an interesting association phenomenon. The chemical shifts of the compound depend on the temperature and the concentration. Only at a concentration of 10^{-6} mol L^{-1} or less, as well as at temperatures above 100°C with higher concentration (10^{-3} mol L^{-1}), does the solution contain only monomeric molecules of **63** [34]. This aggregation of **63** is similar to that observed by Müllen et al. for a very large polycyclic aromatic hydrocarbon [35], and apparently is due to energetically favorable π -stacking.

Upon reduction with potassium in $[\text{D}_8]$ -tetrahydrofuran, the tetraindenopyrene **63** undergoes clean reduction to a dianion which is characterized by a sharp peak at 9.09 ppm in the ^1H NMR spectrum (Scheme 16). Further reduction leads to a radical trianion, which forms a covalent dimer with a C,C-single bond between carbon atoms C9 of two moieties. This dimerization is reversible, as further reduction eventually generates a tetraanion; however, only weak signals of this species could be recorded, and thus an assignment of its structure has not been possible.

The examples presented above demonstrate convincingly once again that modern metal-catalyzed cross-coupling reactions [1,2] open up new avenues to theoretically interesting molecules and materials with unprecedented physical properties. These new opportunities will be further exploited in the near future, and an end to this development is not in sight.



Scheme 16 Reduction of tetrakis(*tert*-butylindeno)pyrene with potassium in $[\text{D}_8]$ -tetrahydrofuran [34].

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