C_{60} Hexakisadducts with an Octahedral Addition Pattern − A New Structure Motif in Organic Chemistry

A. Hirsch,*[a] and O. Vostrowsky[a]

Dedicated to Prof. Hans Jürgen Bestmann on the occasion of his 75th birthday

Keywords: Fullerenes / Cycloadditions / Nucleophilic additions / Cyclizations / Template synthesis

Hexakisadducts, with T_h-symmetrical addition patterns, of C_{60} buckminsterfullerene can be obtained by means of cycloadditions, solid state reactions and nucleophilic cyclopropanations, including a variety of template and tether techniques. C_{60} — or a precursor adduct — serves as a core building block for elaboration into a pseudo-octahedral architecture; an aesthetically pleasing structure motif unique in organic chemistry. The fullerene core can be systematically embellished with one or more different types of addends, giving rise to the formation of uniform or mixed hexakisadducts, respectively. The regioselective exohedral chemistry of C_{60} may serve to provide soluble fullerene derivatives, lipofullerenes, dendrimers, charge-transfer systems, globular amphiphiles and compounds with interesting chemical, physical, biological and material properties.

Introduction

Covalent exohedral fullerene chemistry is a steadily growing field in synthetic organic chemistry.[1,2] During the last decade many important achievements have been made, and many principles of fullerene reactivity are now well established.[1c] The most important method for exohedral functionalization is cycloaddition to [6,6] double bonds in the fullerene core. As well as monoadducts, many stereochemically defined multiple adducts containing, for example, between two and six addends have been synthesized. Of these

[a] Institut für Organische Chemie,
Universität Erlangen-Nürnberg,
Henkestraße 42, 91054 Erlangen, Germany
Fax: (internat.) +49-9131/852-6864
E-mail: andreas.hirsch@organik.uni-erlangen.de

Andreas Hirsch was born in Esslingen, Germany, in 1960. He studied chemistry at the University of Tübingen, Germany, where he obtained his PhD in 1990 under Michael Hanack. He has carried out postdoctoral research at the Institute for Polymers and Organic Solids in Santa Barbara, California, with Fred Wudl. In 1991 he subsequently returned to Tübingen as research associate at the Institute for Organic Chemistry. After his Habilitation in 1994 he joined the faculty of the Department of Chemistry at the University of Karlsruhe as a professor. Since October 1995, he has been Full Professor of Organic Chemistry at Friedrich-Alexander-Universität, Erlangen-Nürnberg. Andreas Hirsch's main research activities have been focussed on the development of methodologies for efficient syntheses of exohedral derivatives of fullerenes and the use of such compounds as structural templates and building blocks for supramolecular architectures and nanomaterials. Other research interests are in the area of dendrimers, calixarene conjugates, new alkynes, new types of synthetic lipids and amphiphiles, model compounds for photoinduced charge separation, chemical derivatization and solubilization of carbon nanotubes, including the investigation of their synthetic potential and properties as new materials.

Otto Vostrowsky was born in 1944 in Vienna, Austria. He received his chemical education at the University of Vienna, Austria, where he obtained his PhD in 1971 at the Institute for Organic Chemistry with M. Pailer. In 1972 he took up a postdoctoral position at the Department of Organic Chemistry at Friedrich-Alexander-Universität, Erlangen-Nürnberg with H. J. Bestmann, where he is working as Akademischer Oberrat with Andreas Hirsch (see above). His main research interests have included synthetic phosphorus chemistry, the structure elucidation and synthesis of insect pheromones, the analysis of essential oil substituents and components of plants, the use of semiochemicals and plant constituents as an integrated tool in pest management and protection of the environment, general natural product chemistry and mass spectrometry as an analytical tool in life sciences. In recent time, his research goals have shifted to the chemistry of fullerenes and nanomaterials and the synthesis and properties of new lipid materials based on fullerenes.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

  1434−193X/01/0305−0829 $ 17.50+.50/0

multiple addition products, hexakisadducts with a T_h-symmetrical octahedral addition pattern are of special interest

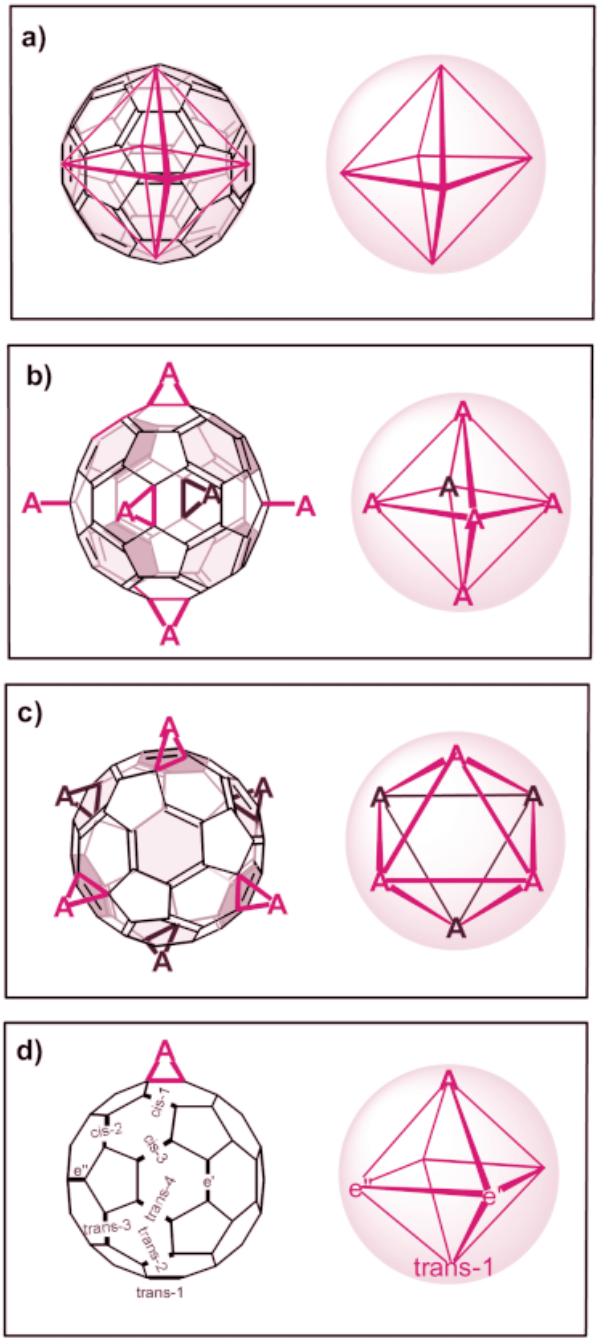


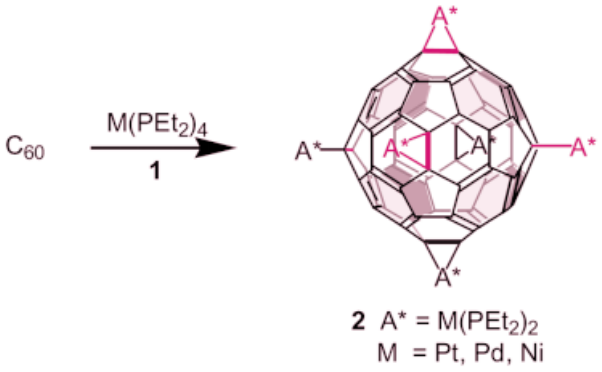
Figure 1. a) VB-Structure of C_{60} including a selected array of 6 pseudooctahedral [6,6] double bonds and schematical representation of the T_h-symmetrical substructure; b) and c) two different views of the octahedral addition pattern of a hexakisadduct of C_{60}; A = e.g., $-CR_2-$, $-CH_2-NH-CH_2-$, $-CH_2-CR=CR-CH_2-$; d) relative positional relationships of [6,6] bonds in a C_{60} adduct

(Figure 1). Their aesthetically pleasing structure motif is unique in organic chemistry. Recently, a variety of methods, including template and tether techniques, have been developed, making them available in decagram quantities.[1,2a−2e] Significantly, it is not only possible merely to introduce one type of addend; different ones can be inserted systematically (Figure 2). The associated synthesis protocols provide a basis for functional fullerene architectural design.

In cases of binding of different addends to octahedral sites, the symmetry of the corresponding mixed adducts is reduced to one of the subgroups of T_h. The type I [3:3] adducts depicted in Figure 2 are inherently chiral, irrespective of the nature of the addends.[3−6]

Hexakisadducts with One Type of Addends

The first synthesis of a T_h-symmetrical hexakisadduct was reported by Fagan and co-workers in 1991.[7] By reacting fullerene with an excess of $(Et_2P)_4M$ **(1)** (Scheme 1; M = Pt, Pd, Ni), they obtained metal complexes of general formula $[(Et_2P)_2M]_6C_{60}$ **(2)**.[7−9] Thermodynamic control of the reaction resulted in pronounced regioselectivity, and so the highly symmetrical hexakisadducts were formed in high yields. A T_h-symmetrical addition pattern was proven unambiguously by X-ray single crystal analysis.[7]



Scheme 1. Synthesis of octahedral metal complexes of general formula $[(Et_2P)_2M]_6C_{60}$ **(2)** (M = Pt, Pd, Ni).[7−9] (front hemisphere addends are marked red, rear hemisphere addends dark)

Three years later, when we systematically investigated the regioselectivity of multiple additions to the [6,6] bonds of C_{60}, we succeeded in the stepwise synthesis of T_h-$C_{66}(COOEt)_{12}$ **4**, by nucleophilic cyclopropanation with diethyl bromomalonate **3** in the presence of NaH as base (Scheme 2).[3,10] The comparatively selective formation of this first purely organic hexakisadduct was possible as attacks to bonds in *e*-positions (relative to already bound addends) are also preferred kinetically.[1]

All the intermediate mono- to pentakisadducts **5−9** (Scheme 2), all incorporating incomplete octahedral addition patterns, were isolated and characterized fully.[10] T_h-$C_{66}(COOEt)_{12}$ **4** is a bright yellow material. Its characteristic electronic absorption spectrum served as a fingerprint for easy structure determination of related hexakisadducts synthesized subsequently, including those with addends of different types. The ^{13}C NMR spectrum of **4** showed only three lines − at δ = 145, 141 (sp^2-C-atoms) and 69 (sp^3-C-atoms) − for the three types of magnetically non-equivalent

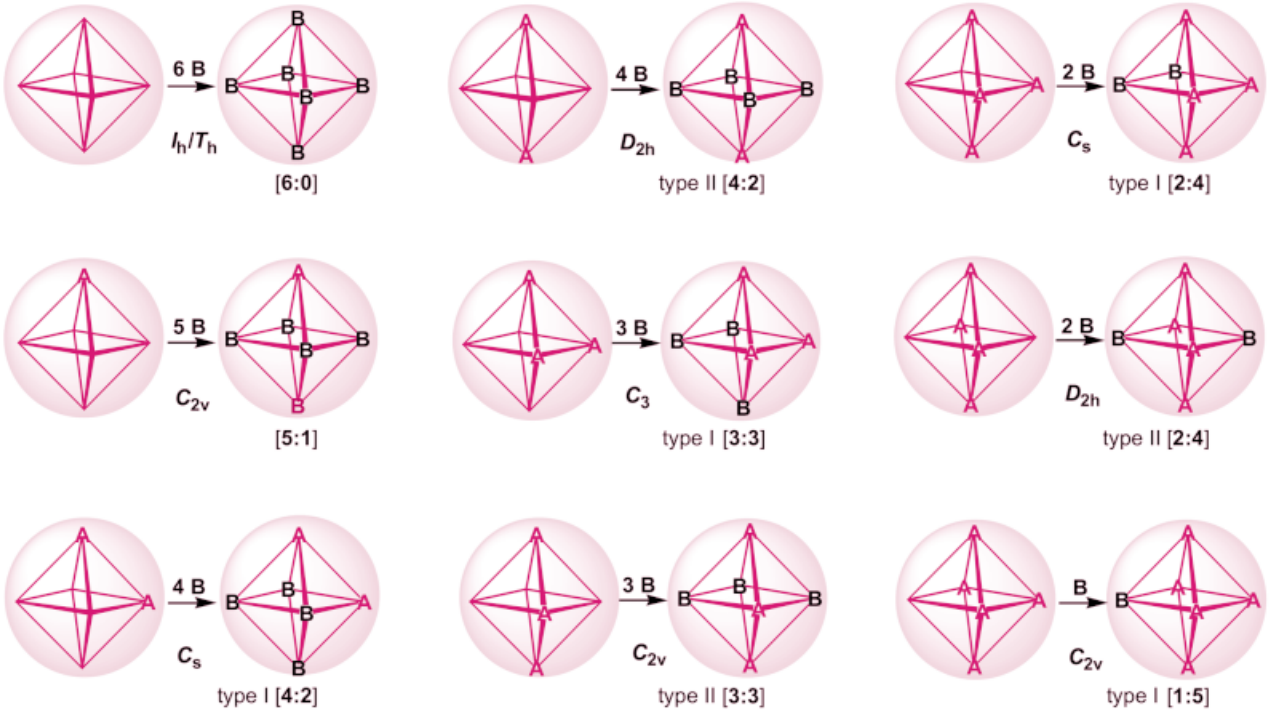
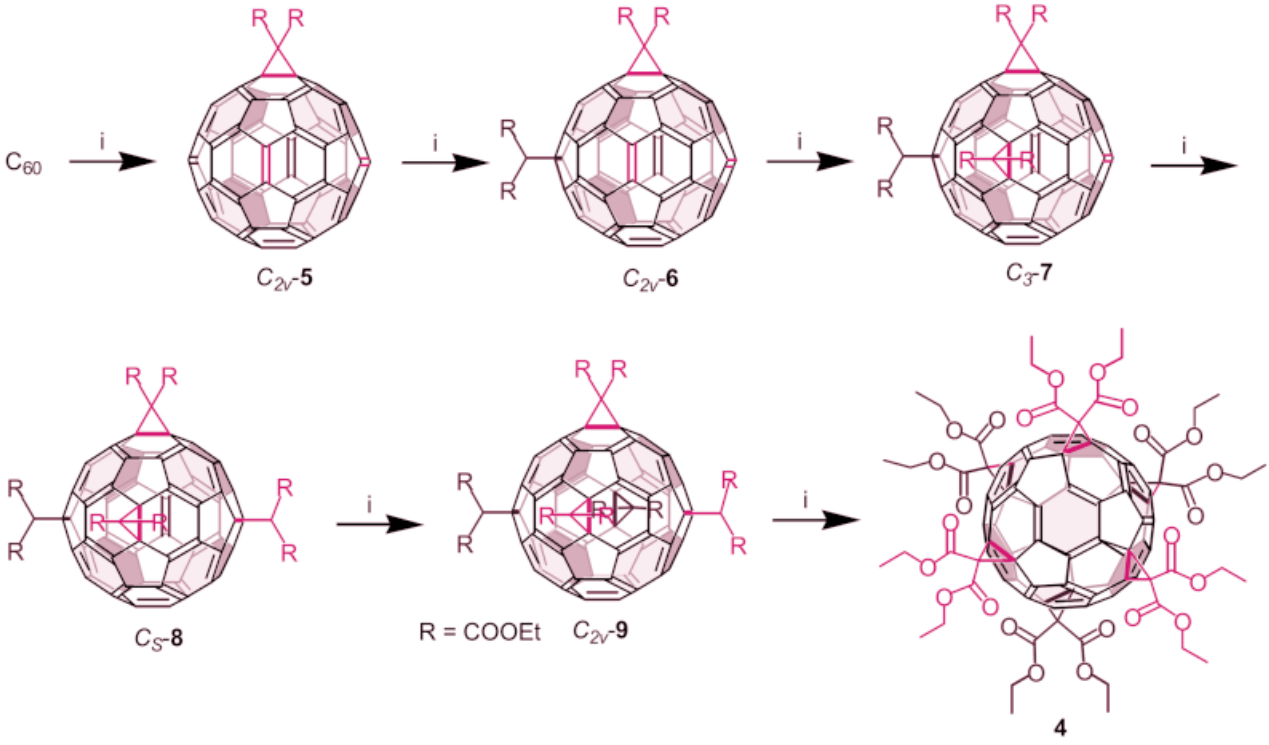


Figure 2. Complete series of octahedral addition patterns in hexakisadducts of C_{60} with one or two different types of addends and their precursor adducts; type I adducts are derived from precursors obtained from successive *e*-additions, type II adducts from precursors synthesized by other means



Scheme 2. Synthesis of T_h-$C_{66}(COOEt)_{12}$ **4** by successive nucleophilic cyclopropanation with diethyl bromomalonate **3**;[3,10] (i: diethyl bromomalonate **3**, NaH; front hemisphere addends are red, rear side addends dark)

C-atoms in the fullerene core. Further unambiguous proof for the aesthetically pleasing structure of **4** was obtained by single-crystal X-ray analysis (Figure 3).[11] Significantly, the aromatic character of the remaining π-electron system, which constitutes a cubic supercyclophane substructure, is enhanced in comparison to that of parent C_{60}. This can be seen in, for example, the less pronounced alternation of [6,6] and [5,6] bond lengths.

One year later, Kräutler and co-workers reported the direct synthesis of the hexakisadduct **10**, formed in 26% yield

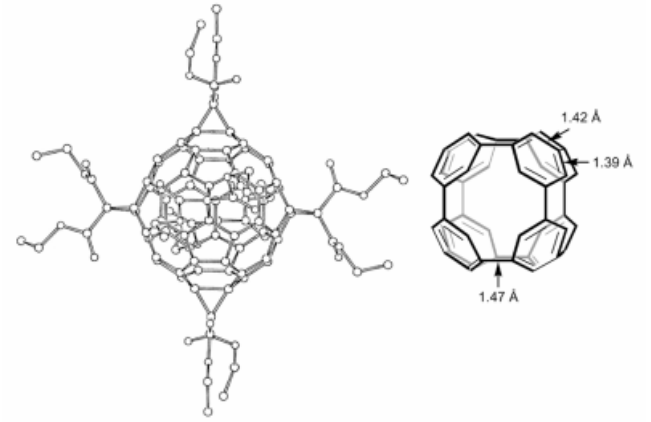
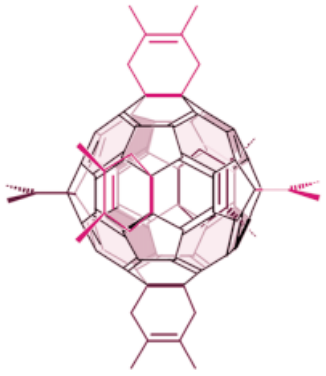


Figure 3. Single-crystal X-ray analysis of T_h-symmetrical $C_{66}(COOEt)_{12}$ **4**[11] and cyclophane substructure of the remaining π-system, consisting of eight benzenoid rings

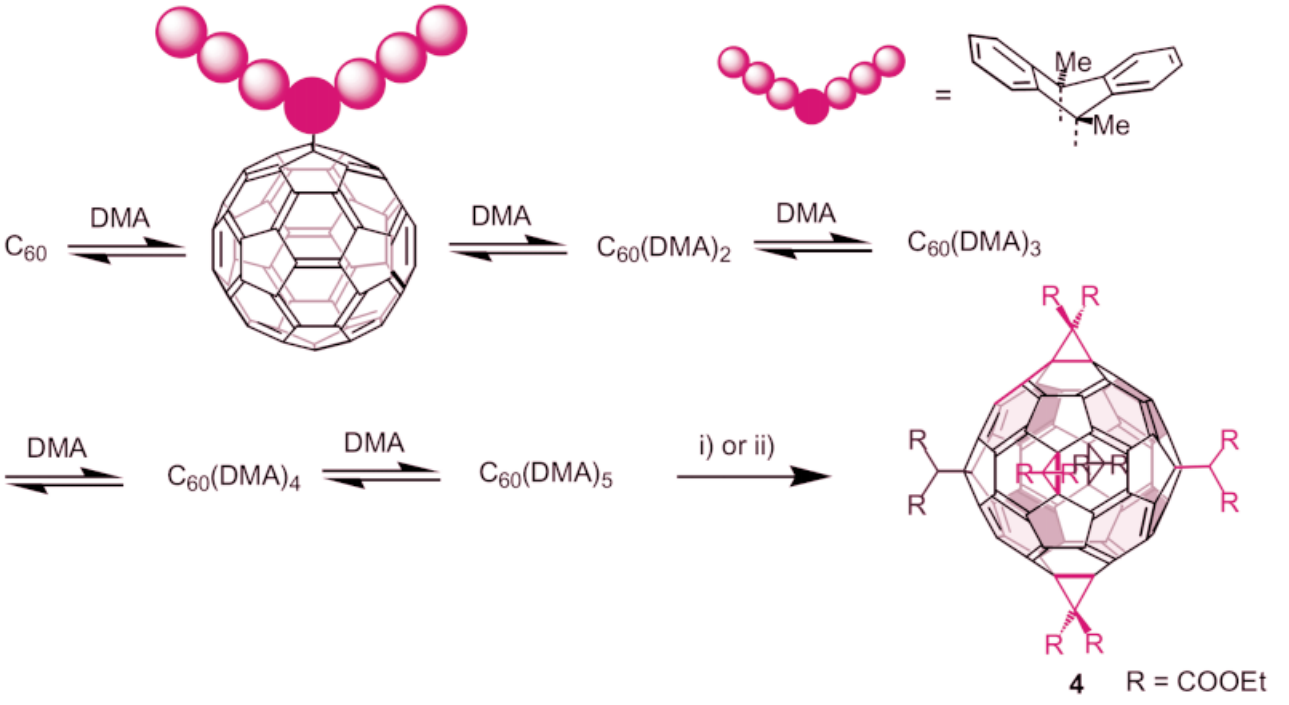


10

by a sixfold [4+2] cycloaddition of C_{60} with an excess of 2,3-dimethyl-1,3-butadiene.[12]

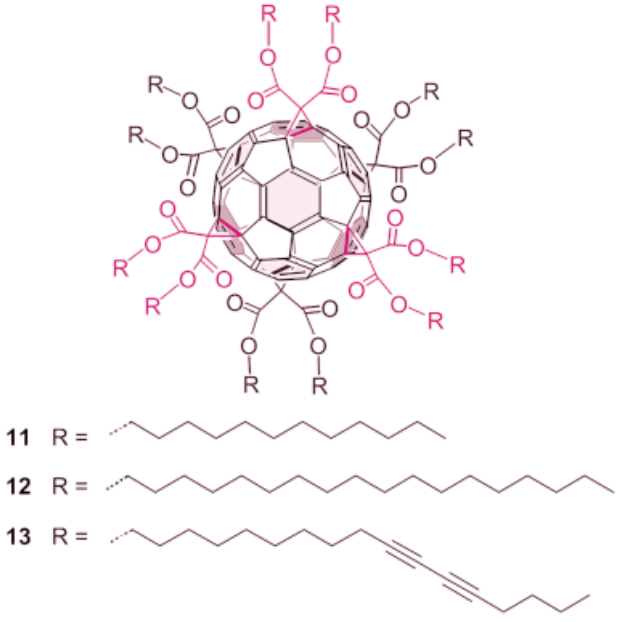
To improve the yield of six-times cyclopropanated adducts like T_h-$C_{66}(COOEt)_{12}$ **4**, we developed a very efficient one-pot method (Scheme 3).[1c,11,13,14] The lynchpin of this strategy was the discovery that 9,10-dimethylanthracene (DMA) binds reversibly to C_{60}. Use of, for example, a tenfold excess of DMA results in an equilibrium between the various $C_{60}DMA_n$ adducts, with *e,e,e*-$C_{60}DMA_3$ as the main component. Hence, synergetic combination of kinetic and thermodynamic control could result in the generation of templates like *e,e,e*-$C_{60}DMA_3$, with incomplete octahedral addition patterns. Since (a) attack of irreversibly binding addends onto such templates occurs with highly pronounced regioselectivity at free octahedral sites, (b) facile rearrangement of DMA addends is possible in *wrong* intermediates, resulting in the formation of an octahedral isomer, and (c) the reversibly bound DMA molecules can easily be replaced by the desired addends, the yields of hexakis-adducts like **4** can be as high as 50%. It has been shown that it is highly advantageous to use DBU as base.[1c,11,13,14] Another important improvement was the in situ formation of the bromomalonates, by DBU-initiated reaction between the corresponding parent malonate and CBr_4.[14] As a consequence, a broad variety of easily available malonates can be used directly for the synthesis in large quantities of T_h-$C_{66}(COOR)_{12}$.

These synthetic improvements were important for securing access to quantities large enough to permit investigation of the material properties of these unprecedented spherical architectures. In order to study the interactions of such systems with lipid membranes, we synthesized the lipofuller-

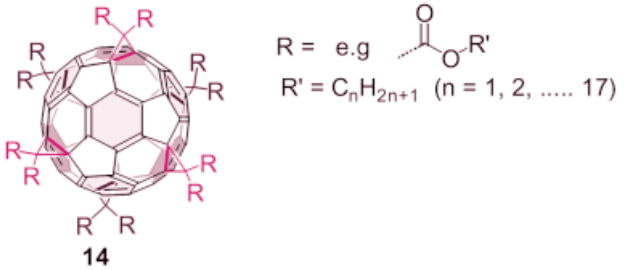


Scheme 3. Template mediation technique using DMA as equilibrating addend.[11,14] (i: diethyl bromomalonate **3** in the presence of DBU,[11] ii: in situ formation of bromomalonate using diethyl malonate and CBr_4/DBU[14])

enes **11** and **12**.[15] These lipofullerenes have been shown, during the intercalation into multilamellar vesicles (MLVs) of dipalmitoyl-*sn*-glycero-3-phosphatidylcholine (DPPC), to self-assemble within bilayers into rod-like structures of nanoscopic dimensions. The dynamics, structure and thermotropic behaviour of this unprecedented type of membrane composite have been studied by means of microcalorimetry, deuterium NMR and X-ray scattering.[15,16] The spherical lipofullerenes show a pronounced tendency toward spontaneous formation of spatially anisotropic superstructures, which may be of importance for future membrane technology.[16] In order to polymerise aggregates of lipofullerenes, we synthesized the functional lipofullerene **13**, containing six pairs of dioctadeca-10,12-diynyl chains. After intercalation of **13** in DPPC vesicles, a photochemically induced polymerization was carried out. Perfectly spherical fullerene-nanospheres were generated.[17]

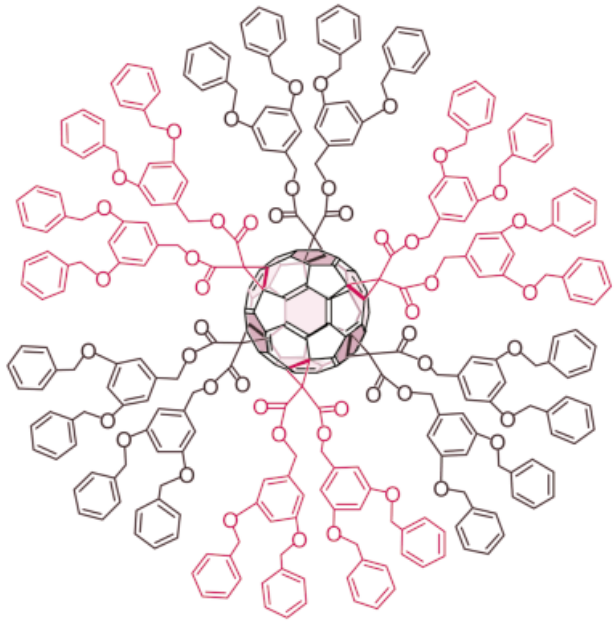


Significantly, the lipofullerenes **11** and **12** have very low melting points — 22 and 67 °C (DSC, heating scan), respectively — with **11** being the first fullerene derivative liquid at room temperature.[15] Moreover, below the melting point they undergo a phase transition into a second, more densely packed solid phase. These observations prompted us to investigate systematically the dependence of the thermotropic behaviour of T_h-$C_{66}(COOR)_{12}$ on the nature of the alkyl chain R, and to synthesize the adducts **14**.[18]

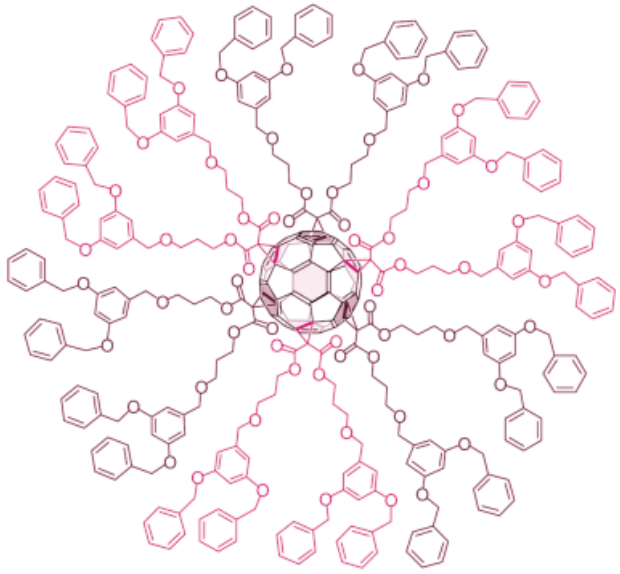


14

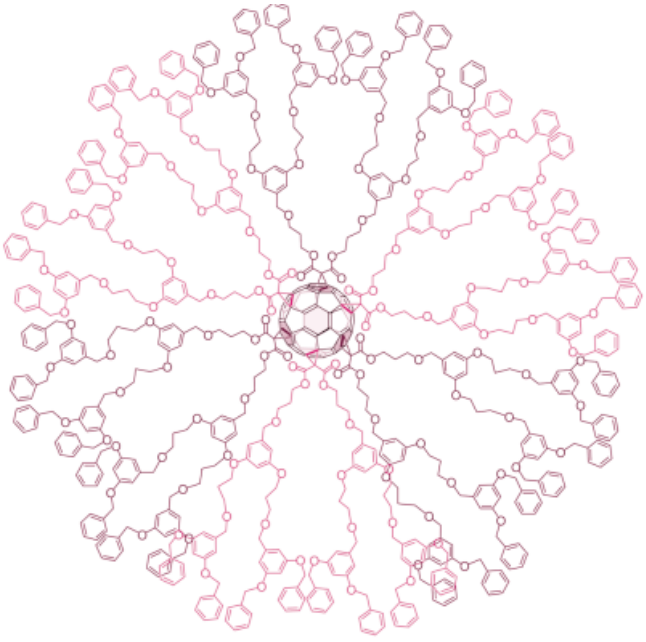
The T_h-symmetrical sextuple addition pattern also represents an attractive core tecton for dendrimers.[19] If R in T_h-$C_{66}(COOR)_{12}$ is a dendritic chain, it is possible to imagine spherical dendrimers with a core branching multiplicity of 12, even if low generation dendra are employed. As examples for this new dendrimer prototype, we employed our template mediation technique to synthesize **15**–**17**,[19,20] containing dendrons based on benzyl ethers, in one step, starting from the corresponding dendritic malonates. Since, thanks to their additional spacer units, the



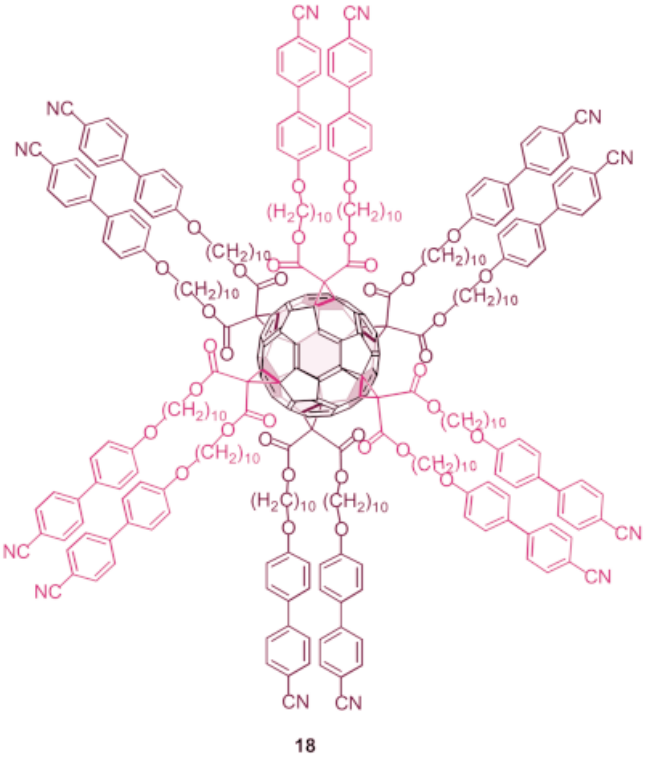
15



16



17

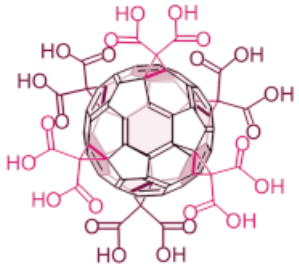


18

dendra in **16** and **17** give rise to less steric hindrance, yields for the convergent malonate addition were much higher in those cases than for **15**.[20]

Addition of six mesotropic cyanobiphenyl malonate addends produced the spherical thermotropic liquid crystal **18**. DSC and POM investigations revealed a smectic A phase between 80 and 133 °C.[21] It is interesting to note that this spherical and highly symmetrical compound gives rise to liquid crystallinity despite the absence of molecular anisotropy.

Fullerene malonates $C_{66}(COOR)_{12}$ can serve as valuable starting materials for further side chain modification. This has been demonstrated in, for example, the synthesis of the highly water-soluble hexamalonic acid derivative $C_{66}(COOH)_{12}$ **19** by hydrolysis of **4**.[11] A more efficient synthetic route to water-soluble fulleroderivatives is cyclopropanation of C_{60} with bis(3-*tert*-butoxycarbonyl)propyl malonate **20** to afford the *tert*-butyl ester **21** (Scheme 4). Subsequent cleavage of the *tert*-butyl protecting group leads to the spherical dodecacarboxylic acid **22**, which can then be transformed into polyglycine adduct **23**.[22] The synthesis of stereochemically defined, water-soluble C_{60} adducts is an important requirement for the investigation of biological activities of fullerene derivatives.[23]

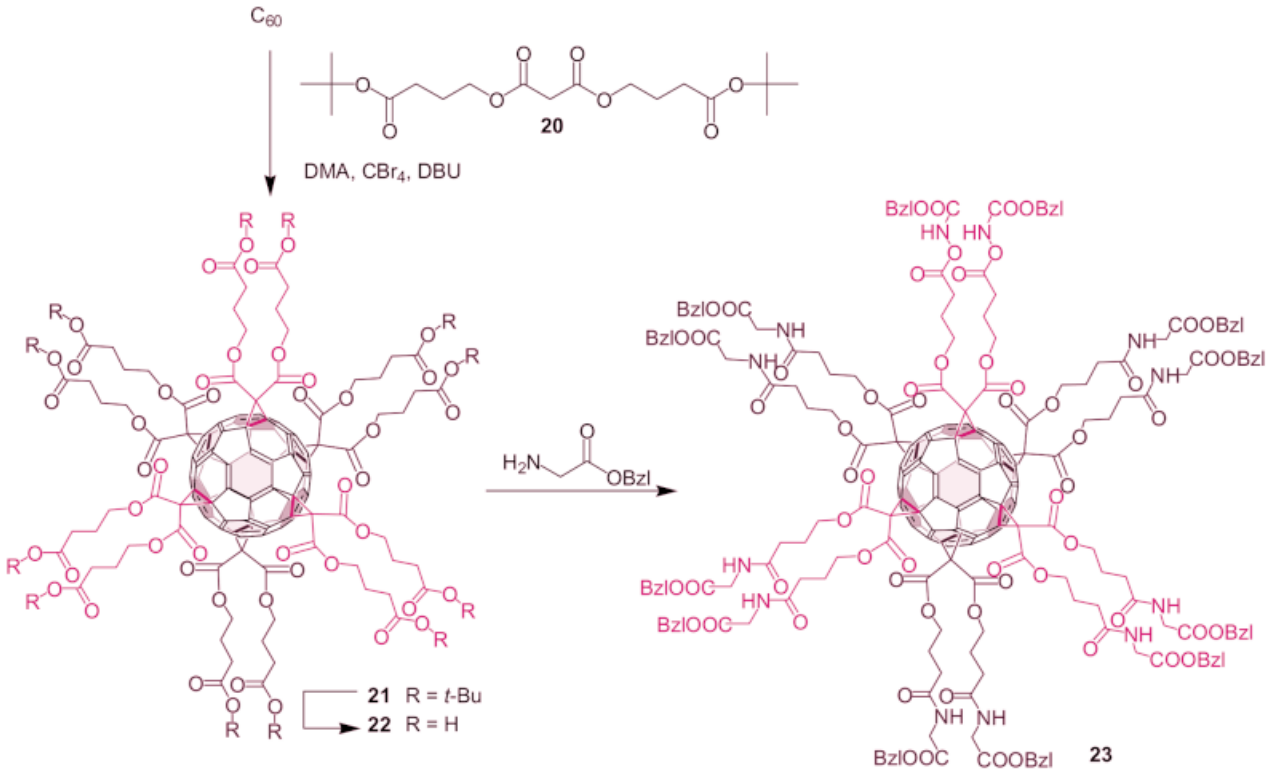


19

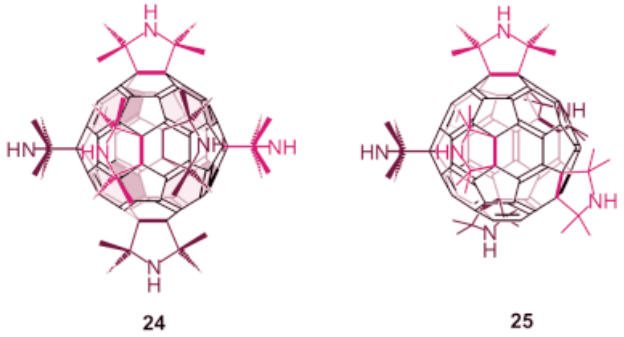
In an attempt to synthesize T_h-symmetrical fulleropyrrolidine hexanitroxide as a candidate three-dimensional ferrimagnet, Rubin et al. [24] investigated the sextuple [3+2] dipolar cycloaddition of azomethine ylides to C_{60}. The sterically demanding tetramethyl azomethine ylide, generated from dry acetone and 2,2-dimethylglycine in chlorobenzene, showed high selectivity in the stepwise series of [3+2] cyclizations leading to the T_h symmetrical hexakisadduct **24**[24] in 12% yield. In contrast to the malonates $C_{66}(COOR)_{12}$ (R = H, alkyl), **24** exhibited some unusual optical properties, such as a large fluorescence quantum yield of 0.18 in methylcyclohexane and an intense and bright orange phosphorescence, with a lifetime of 4.4 sec, if this solution was cooled to 77 K.[24,25] Another unexpected outcome of the associated synthetic efforts was the formation of a second inherently chiral hexakisadduct **25** with D_3-symmetry, isolated in 61% yield by crystallization from the mother liquors of the **24** crystallization batches.[24]

Mixed Hexakisadducts with Different Types of Addends

Hexakisadducts that contain different addends at different octahedral sites and whose symmetry belongs to a sub-



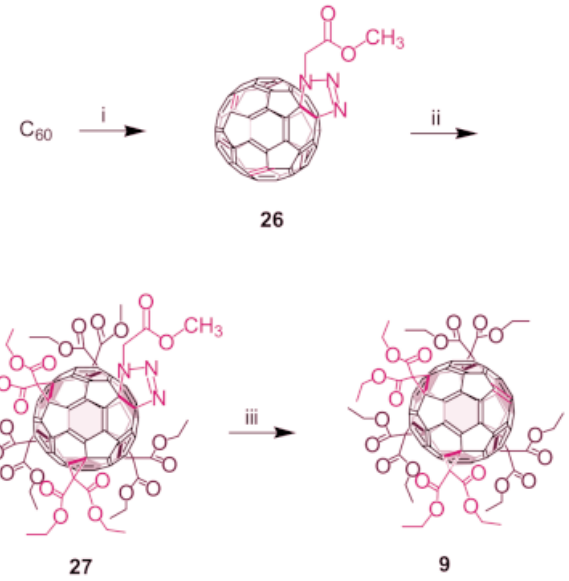
Scheme 4. Synthesis of highly water-soluble dodecacarboxylic acid **22** and protected polyglycine derivative **23**[22]



group of T_h are very attractive synthesis goals. The major challenge is to address the octahedral positions of the C_{60} core specifically. A number of strategies for the synthesis of defined hexakisadducts have been developed recently. All these methods are based on the use of oligoadducts with an incomplete octahedral addition pattern as starting materials. These precursor molecules can be obtained, for example, by successive and regioselectively favoured *e*-additions,[1c] by topologically controlled solid state reactions[26] or by tether functionalization methods.[2b,2c] Mixed hexakisadducts with up to four different types of addends, including some with inherently chiral addition patterns, have been synthesized. This unique means of organic scaffolding has provided facile access to new functional macromolecules like globular amphiphiles,[27] redox-active dendrimers[20] and biofunctional transmembrane anchors.[28]

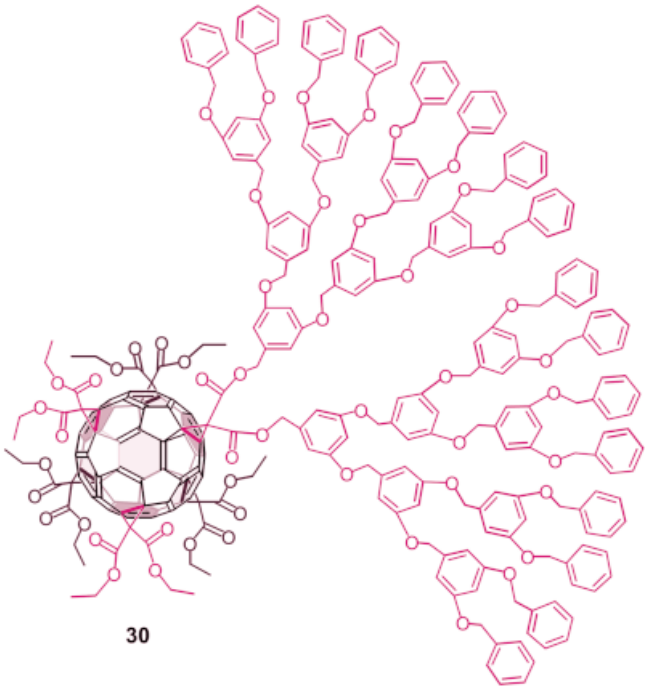
Mixed Hexakisadducts with Two Different Types of Addends

The possible structures of mixed hexakisadducts with two different addends in octahedral positions are depicted in



Scheme 5. Protection-deprotection technique for the synthesis of *e*-pentakisadduct **9**;[13] (i: methyl azidoacetate, 1-chloronaphthalene, 60 °C; ii: 10 equiv. DMA, diethyl bromomalonate, DBU, toluene, room temp.; iii: toluene, reflux)

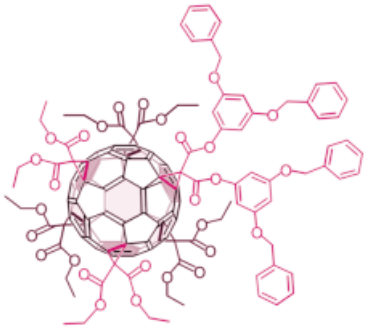
Figure 2. The most important aspect is the synthesis of precursor adducts possessing an incomplete octahedral addition pattern with one type of addend. Whereas monoadducts or *e*-bisadducts are easily available, the production of*trans*-1-bisadducts or higher adducts with incomplete addition requires more effort. However, production of the mixed hexakisadducts from all the precursors is in general straight forward, since advantage can be taken of either the effective template mediation technique or the highly pronounced *e*-regioselectivity characteristic of higher adducts[1] to complete the octahedral addition pattern.



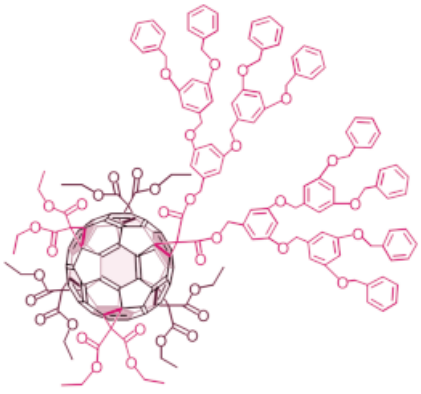
30

Mixed [5:1] Hexakisadducts

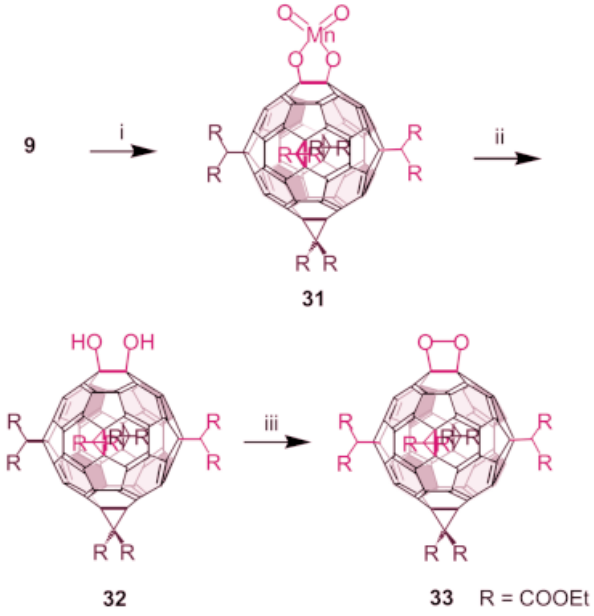
This addition pattern is accessible by starting either from a pentakisadduct with one unchanged octahedral site or from a monoadduct with five unoccupied sites. Pentakisadducts like **9**, with a C_{2v}-symmetrical addition pattern, can be synthesized stepwise by successive *e*-addition and isolation of each precursor adduct **5**, **6**, **7** and **8**.[10] However, this procedure is very time-consuming and the overall yield is not satisfactory. For a convenient synthesis of this adduct type, we developed an effective protection-deprotection strategy (Scheme 5). The reaction sequence starts with the synthesis of the triazoline **26** by [3+2] cycloaddition of methyl azidoacetate onto a [6,6] double bond of C_{60}. After exhaustive template-mediated cyclopropanation to **27** and thermally induced [3+2] cycloreversion, the pentakisadduct **9** was obtained in good overall yield.[13]



28



29

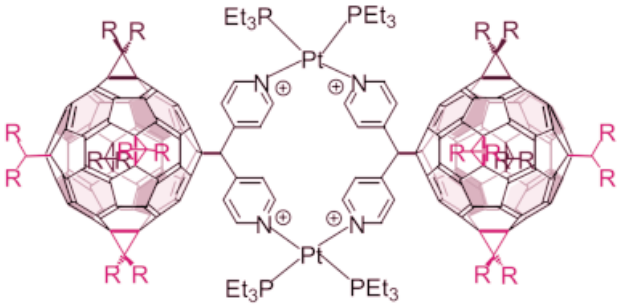


Scheme 6. Synthesis of manganate **31** and dioxetanofullerene **33**;[13] (i: $KMnO_4$, 18-DBC-6; ii: CH_3COOH; iii: $Pb(OAc)_4$)

This pentakisadduct is a very valuable starting material, because attack at the remaining octahedral [6,6] double bonds proceeds with quantitative regioselectivity. Examples of [5:1] hexakisadducts originating from **9** are the dendrimers **28**, **29** and **30**,[29] and manganate ester **31** (Scheme 6).[13] The reason for the synthesis of **31** was an attempt to open the fullerene cage oxidatively. However, hydrolysis of **31** to **32** with subsequent $Pb(OAc)_4$ treatment afforded the dioxetane **33** instead of the desired cluster-opened diketone.[13]

The inverse reaction sequence starting from easily available [6,6] monoadducts, which are subsequently transformed into [1:5] hexakisadducts using the template mediation technique, has been shown to be even more efficient.

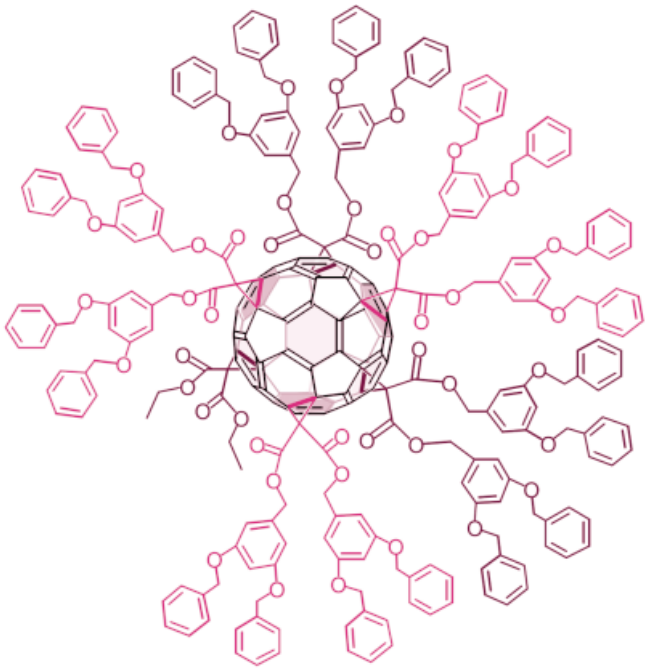
This has already been demonstrated in the synthesis of the triazoline **27**. Further examples are the fulleropiperazine **34**,[13] as well as the bis(alkynyl)- and bis(pyridinyl)-derivatives **35**[30] and **36**.[31] Diederich and co-workers transformed



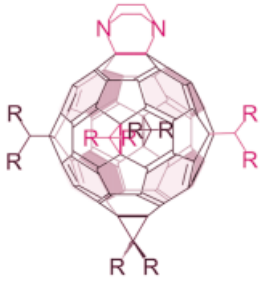
37

4 $^-$OTf

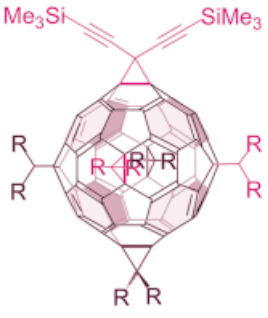
R = COOEt



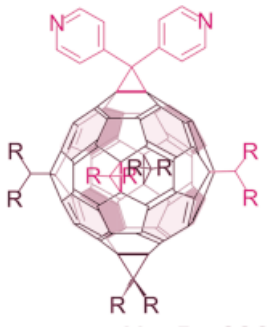
38



34 R = COOEt

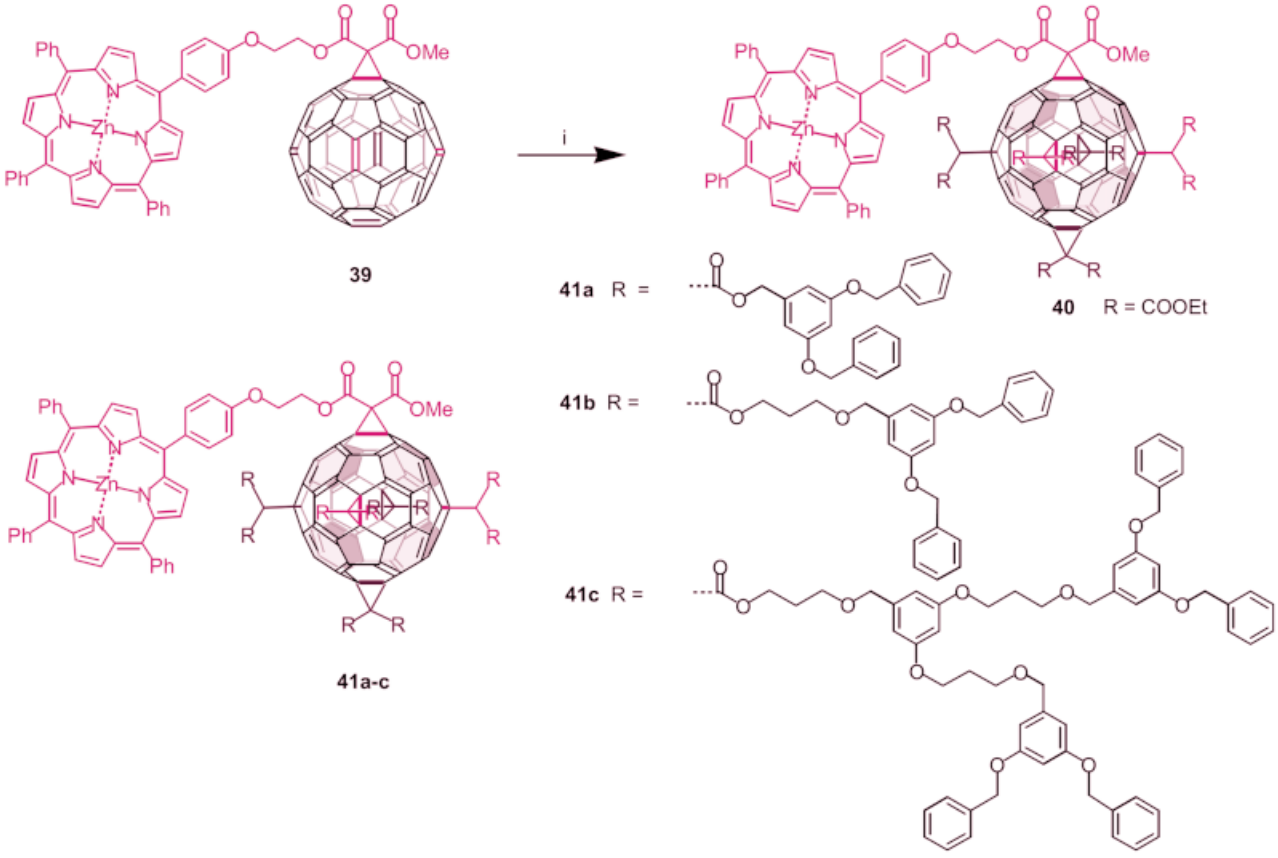


35 R = COOEt

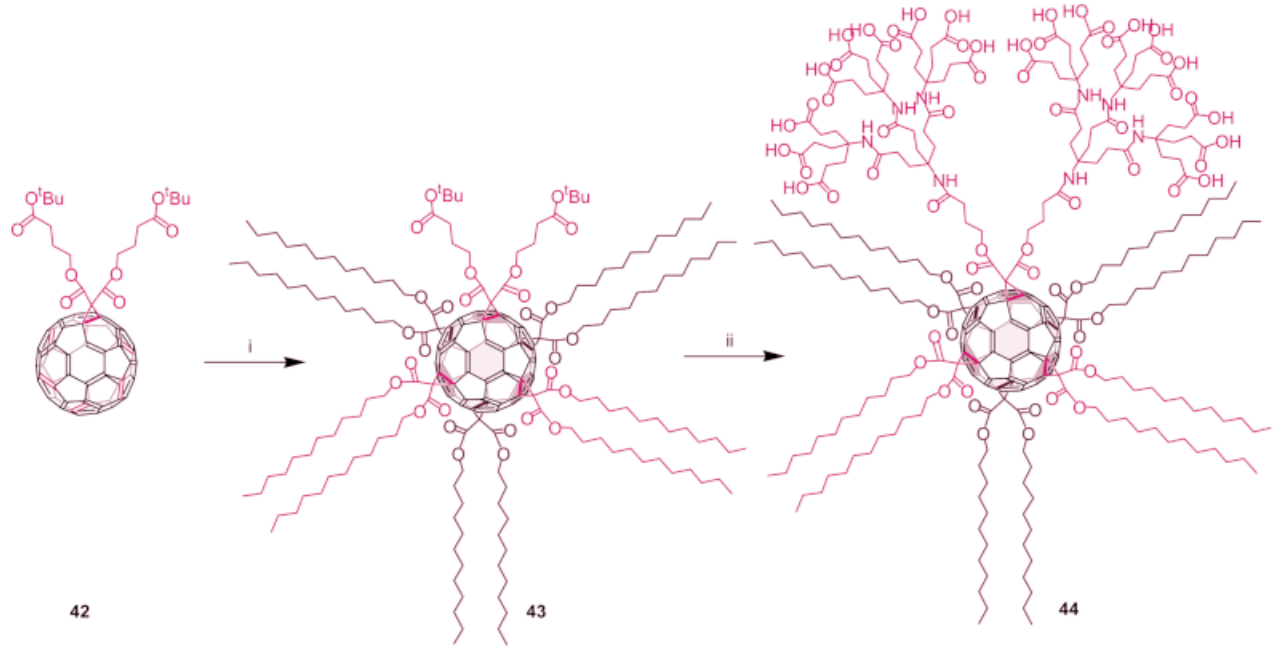


36 R = COOEt

36 into the supramolecular cyclophane **37** in quantitative yield by mixing equimolar amounts of **36** with *cis*-[Pt-$(PEt_3)_2(OTf)_2$].[31]An addition pattern inverse to that seen with **28** was accomplished by the synthesis of **38**, by convergent attachment of five benzyl ether dendra to the monoadduct **5**.[19] Similarly, we succeeded in the synthesis of the [5:1] mixed fullerene-porphyrin adduct **40** and dendrimers **41a–c**, by fivefold cyclopropanation of the porphyrin monoadduct **39** (Scheme 7).[20] Addition of the comparatively compact Fréchet-type,[32] first generation (G1) bromomalonate in the presence of 10 equ. DMA/DBU resulted in



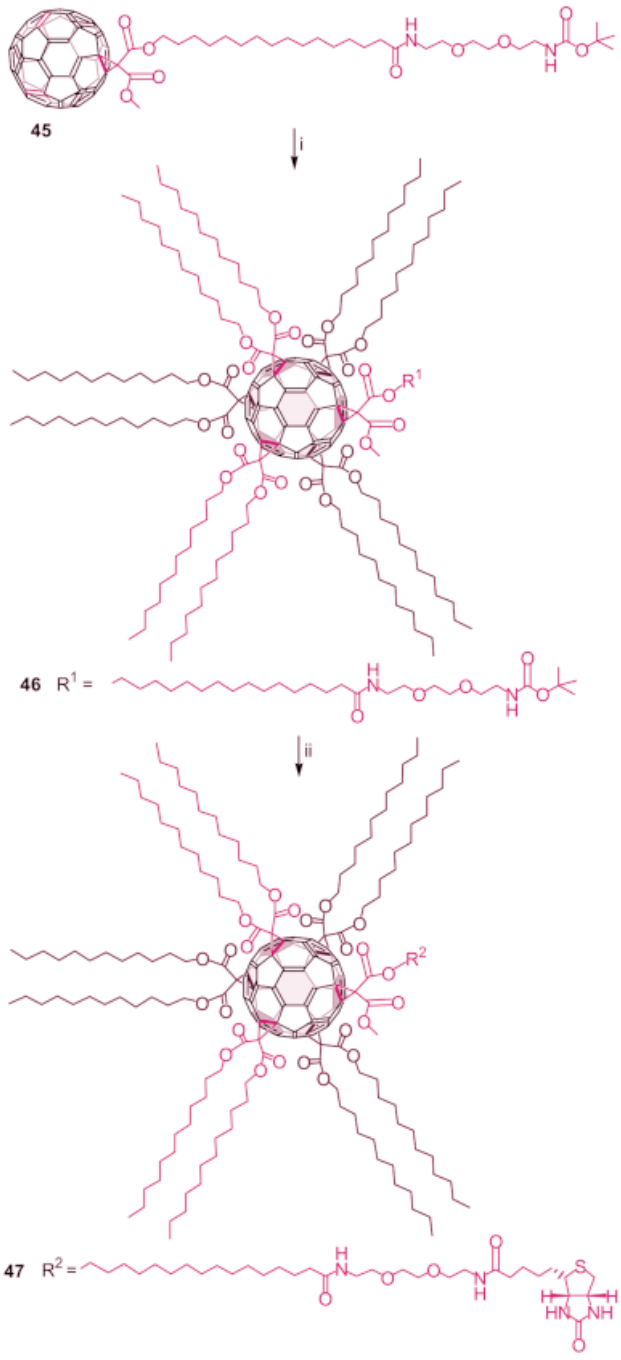
Scheme 7. Synthesis of porphyrin-fullerene [1:5] mixed hexakisadduct **40** and dendrimer-porphyrin-fullerenes **41a−c**;[20] (i: DMA, ethyl bromomalonate, DBU)



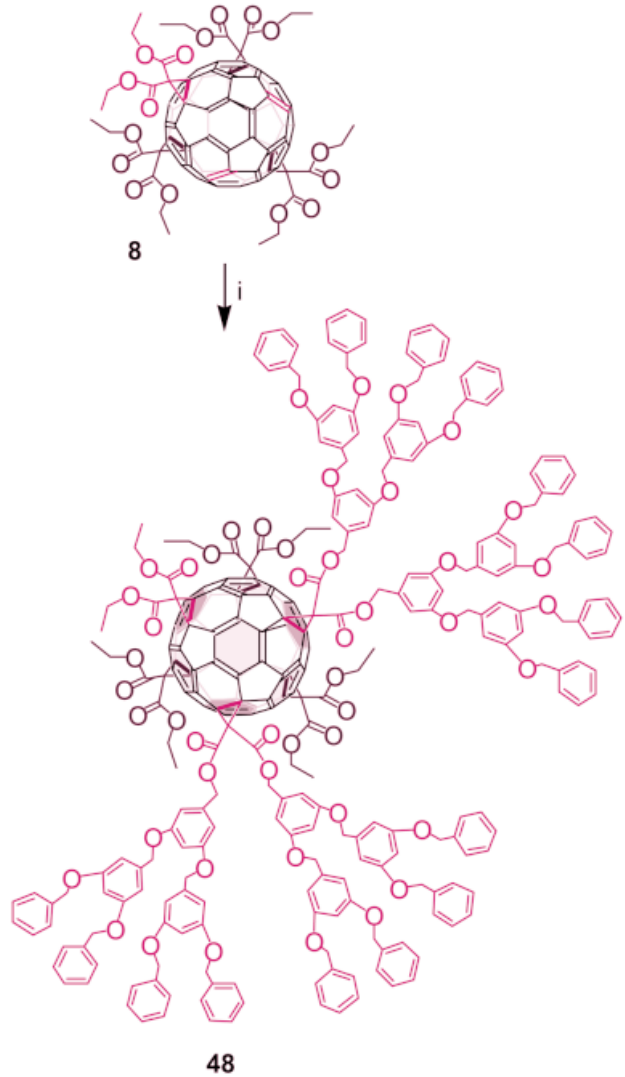
Scheme 8. Synthesis of globular amphiphile **44**;[27] (i: dodecyl malonate, CBr_4, DBU; ii: Newkome-type dendrimer, peptide coupling)

the resulting dendrimer **41a** being obtained in only 2% yield. In order to avoid steric hindrance and to increase the yield of the convergently synthesized functional dendrimers, we employed the same spacer-enlarged dendritic malonate that we had used for the synthesis of **16** and **17**. Consequently, the corresponding cyclopropanations of **39** afforded the mixed hexakisadducts **41b** and **41c** in about 13% and 2% yield, respectively. The influence on the redox potentials of the porphyrin and fullerene moieties of the dend ritic coverage in the functional dendrimers was investigated by cyclic voltammetry.[20]

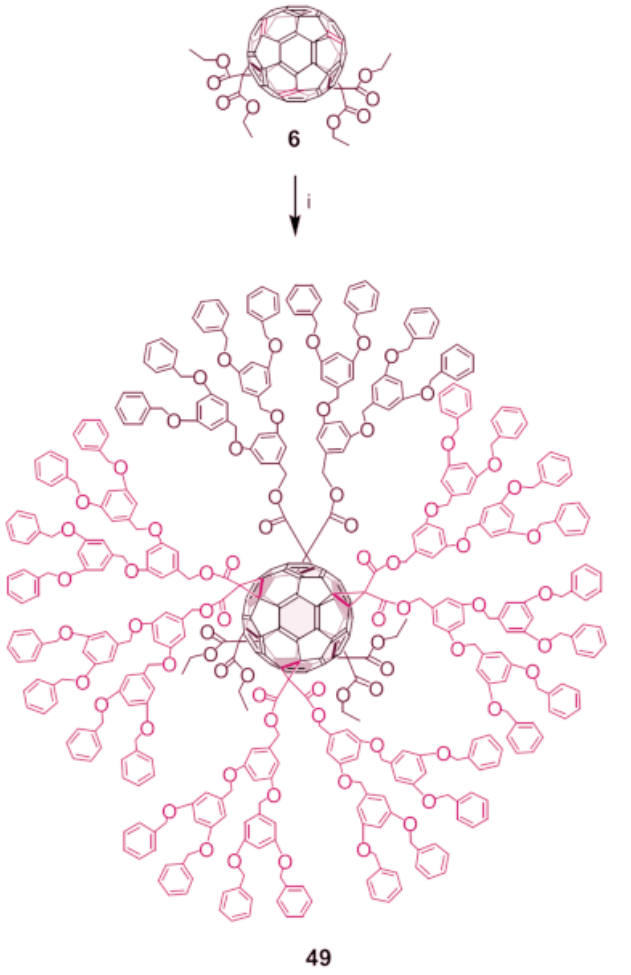
Using a Newkome-type amide dendron[32] as a hydrophilic addend and five didodecyl malonates as lipophilic addends, we recently synthesized a new prototype amphiphile with a spherical structure (Scheme 8).[27] Bis(3-*tert*-butyloxycarbonyl)propyl bromomalonate **20** served as precursor addend in the monoadduct **42**. Subsequent fivefold addition of didodecyl malonate in the presence of CBr_4/DBU resulted in the formation of hexakisadduct **43** in 23% yield. Cleavage of the *tert*-butyl ester with TFA and subsequent amide formation with the second generation amide dendron using typical peptide coupling conditions afforded the amphiphilic hexakisadduct **44**.[27] This globular am-



Scheme 9. Successive cyclopropanation of C_{60}, leading to the hexakisadduct **46**, and final coupling with biotin to give protein anchor lipofullerene **47**[38] (red: front C_{60} hemisphere; dark: rear hemisphere; i: dodecyl malonate, DMA, CBr_4, DBU; ii: TFA/CH_2Cl_2, (+)-biotin/CDI)



Scheme 10. Double nucleophilic cyclopropanation of all-*e*-tetrakisadduct **8** with second generation (G2) Fréchet dendron bromomalonate yields dendrimeric [4:2] hexakisadduct **48**;[29] (i: CHBr(COOG2), DBU, toluene/CH_2Cl_2, 3 d, room temp.)



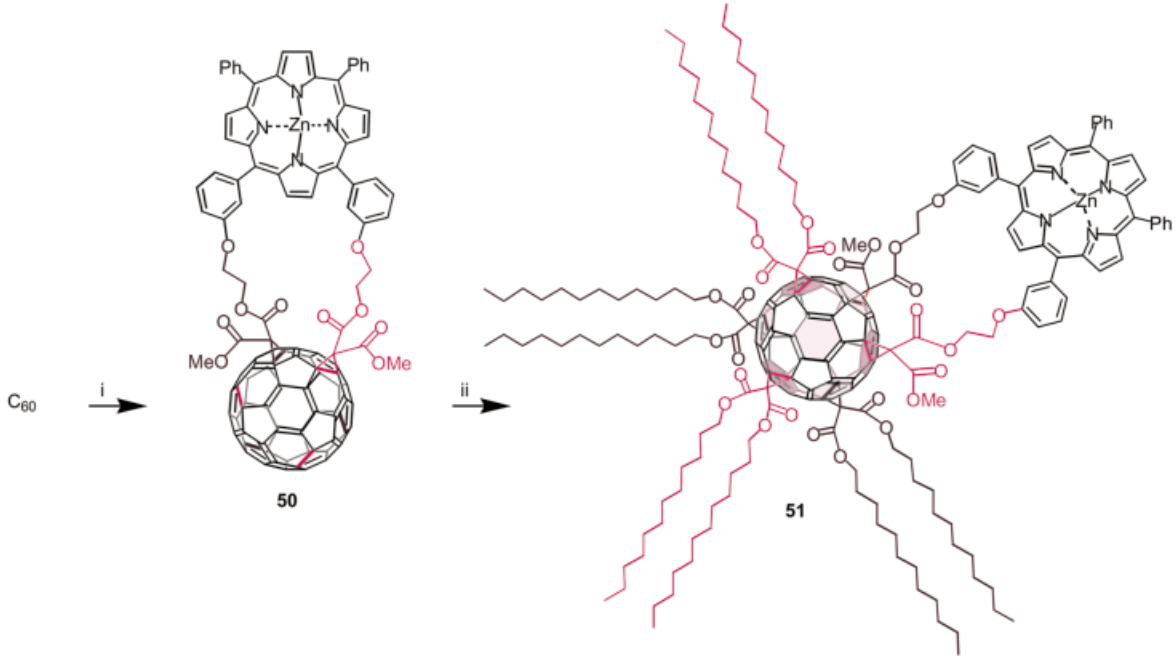
Scheme 11. Template-mediated fourfold cyclopropanation of *e*-bisadduct **5**, leading to hexakisadduct **49**;[29] (i: DMA, second generation (G2) Fréchet dendron bromomalonate CHBr(COOG2), DBU, toluene/CH_2Cl_2, 3 d, room temp.)

phiphile dissolves in water, forming unilamellar vesicles with diameters typically between 100 and 400 nm, and reveals a very small critical micelle concentration (CMC). Stable monolayers of **44** on the air-water interface were produced by the Langmuir-Blodgett technique.[33] Thanks to the presence of 18 carboxylic acid functions which can be deprotonated successively, electrostatic interactions between the spherical amphiphiles can be modified specifically. Electrostatic interactions of monolayers of **44** with cytochrome c at pH values corresponding closely to the surface pK_a (7.4; 8 negative charges per molecule) were investigated by neutron scattering measurements.[33]

As an example of a biofunctional fullerene derivative which is able to intercalate into a DPPC bilayer, we synthesized the biotinated lipofullerene **47**.[28] This molecule can be used as a transmembrane anchor for proteins located outside the membrane (Scheme 9). Cyclopropanation onto C_{60} of an amphiphilic spacer malonate afforded the monoadduct **45** as starting material. In a second cyclopropanation sequence, **45** was treated with didodecyl malonate in the presence of CBr_4, DMA and DBU to give the mixed [1:5] hexakisadduct **46**. A final coupling with biotin resulted in the formation of lipofullerene **47**. The biotin anchor in **47** is able to bind proteins like avidin and streptavidin.[28]

Mixed [4:2] Hexakisadducts

As a suitable starting material for the synthesis of [4:2] mixed hexakisadducts we used the tetrakisadduct **8**, obtained from fourfold cyclopropanation of C_{60} [10] with diethyl malonate. Double cyclopropanation of this precursor core with the second generation (G2) Fréchet-dendron[32] bromomalonate in the presence of DBU afforded C_S symmetrical $C_{66}(COOEt)_8(COOG2)_4$ **48** in 75% yield as a yel-



Scheme 12. [2:4] Zinc-porphyrinato-hexakisadduct **51**;[34] (i: porphyrinobismalonate, CBr_4, DBU; ii: dodecylmalonate, I_2, DMA, DBU)

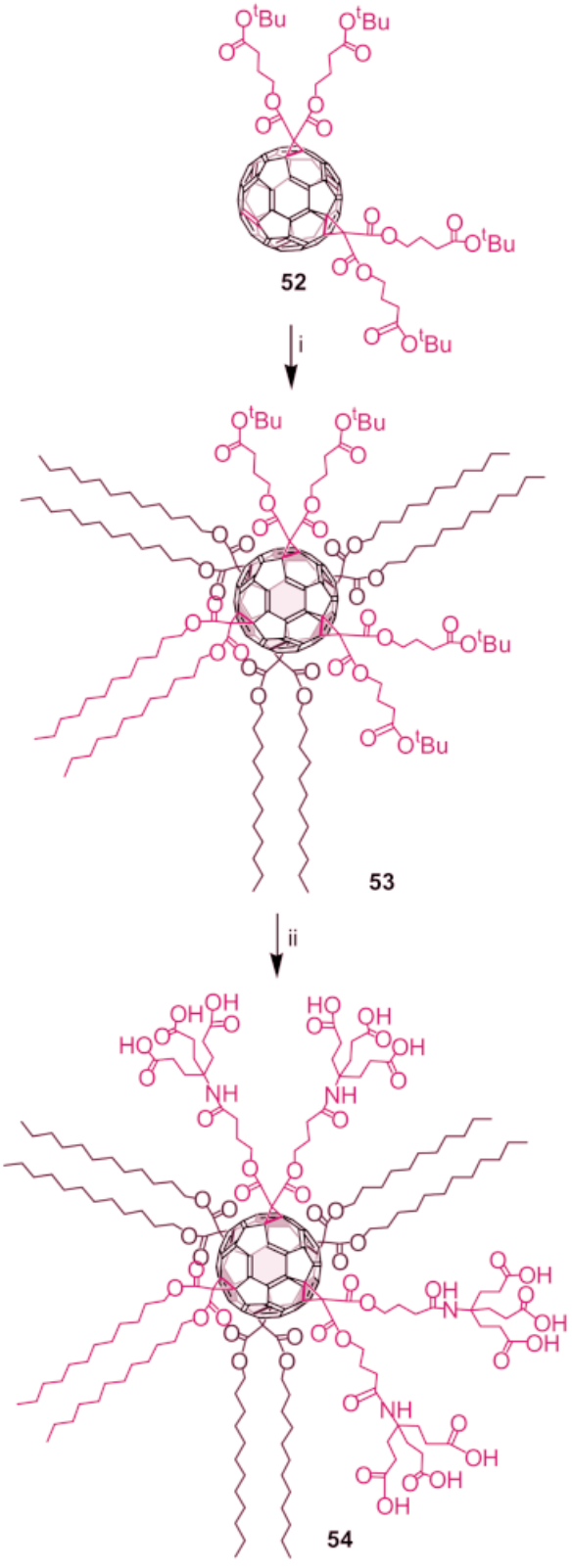
low powder (Scheme 10[29] The inverse [2:4] addition pattern can be obtained by successive fourfold cyclopropanation of the *e*-bisadduct[3] **6** with second generation (G2) dendron bromomalonates to give $C_{66}(COOEt)_4(COOG2)_8$ **49** in 73% yield, also as a bright yellow powder (Scheme 11).[29]

En route to synthesizing fullerene-based architectures with specific electronic properties, we allowed a porphyrinobismalonate to add twice to C_{60}. This reaction afforded the bismethano adduct **50**, with an *e*-addition pattern, as the major reaction product in 12% yield.[34] A subsequent fourfold cyclopropanation with dioctadecyl malonate gave the mixed [4:2] hexakisadduct **51** (Scheme 12).

In a similar fashion, **54** was synthesized starting from the *e*-bisadduct **52** with four protected terminal carboxylic functions (Scheme 13). Subsequently, four didodecyl malonate addends were allowed to react with the remaining octahedral [6,6] double bonds in order to complete the [4:2] addition pattern (**53**). After deprotection of the *tert*-butyl groups, Newkome-type amide (G1) dendra were coupled with the carboxylic groups. The final step was the deprotection of the dendritic termini.[22]

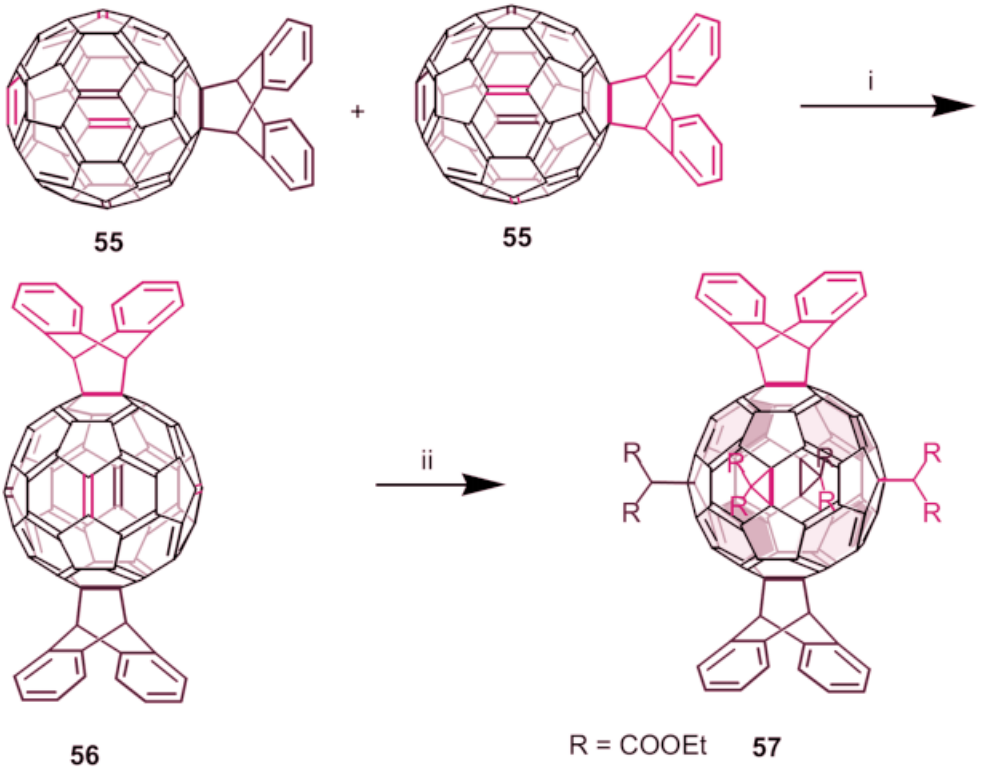
Kräutler and co-workers developed a topochemically controlled, solid-state group-transfer synthesis[26,35] to obtain the *trans*-1-bisanthracene adduct **56**, which can serve as starting material for the synthesis of type II [4:2] addition pattern compounds, in which two addends are bound at the poles and four are attached at the equatorial belt (Scheme 14). The first step was a regiospecific thermolysis of crystalline monoadduct **55** to give a (1:1) mixture of C_{60} and the *trans*-1-bisadduct **56**. The two anthracene addends of **56** served to direct four bromomalonate addends regiospecifically into *e*-positions, giving hexakisadduct **57** in 95% yield. The subsequent thermal removal of the two polar anthracene molecules led to a tetrakisadduct with an equatorial belt on the carbon sphere,[35] representing a valuable tecton for further specific functionalization.

In 1994, Diederich and co-workers reported a very important approach to regioselective formation of multiple adducts of C_{60} by tether-directed remote functionalization.[36] Reversibly removable tethers are used as the primary addends. As a function of their structure, these can occupy distinct addition locations only. As a consequence, they ensure access to certain remaining sites and to a great diversity of three-dimensionally functionalized fullerene building blocks.[2c–2e] Subsequently, the tethers can either be removed from the polyfunctional adducts, or they may be replaced by other functional addends.[36] Using this approach, a [4:2] hexakisadduct **62** with the same addition pattern as **57** has been synthesized (Scheme 15). When a solution of tethered hexakisadduct **58**, the synthesis of which is discussed below, was irradiated in the presence of C_{60} as a $^1O_2$ sensitizer while O_2 was bubbled through, an isomeric mixture of allylic hydroperoxides was obtained; the result of a $^1O_2$-ene reaction.[2c,37] Subsequent reduction to the corresponding allylic alcohols, dehydration (using TosOH) to the bis(cyclohexa-1,3-diene) derivative, and a Diels–Alder/*retro*-Diels–Alder sequence afforded the

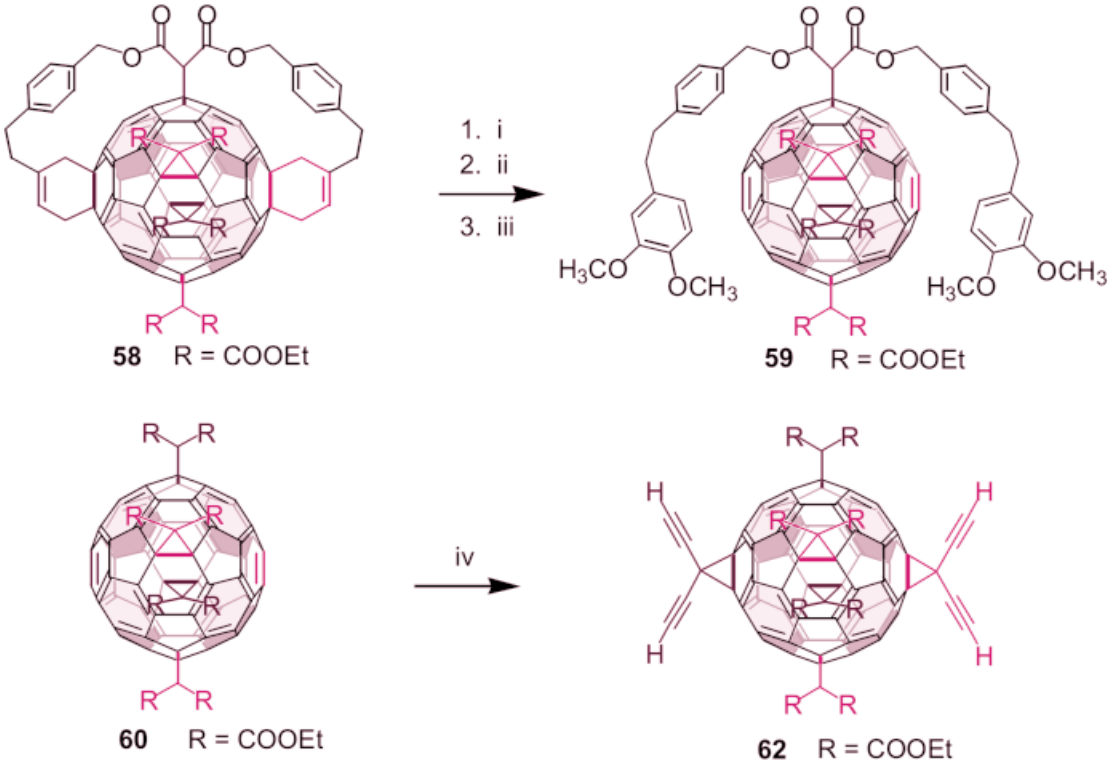


Scheme 13. Synthesis of globular amphiphile **54**;[22] (i: dodecyl malonate, DMA, CBr_4, DBU; ii: TFA, Newkome-type dendrimer, peptide coupling)

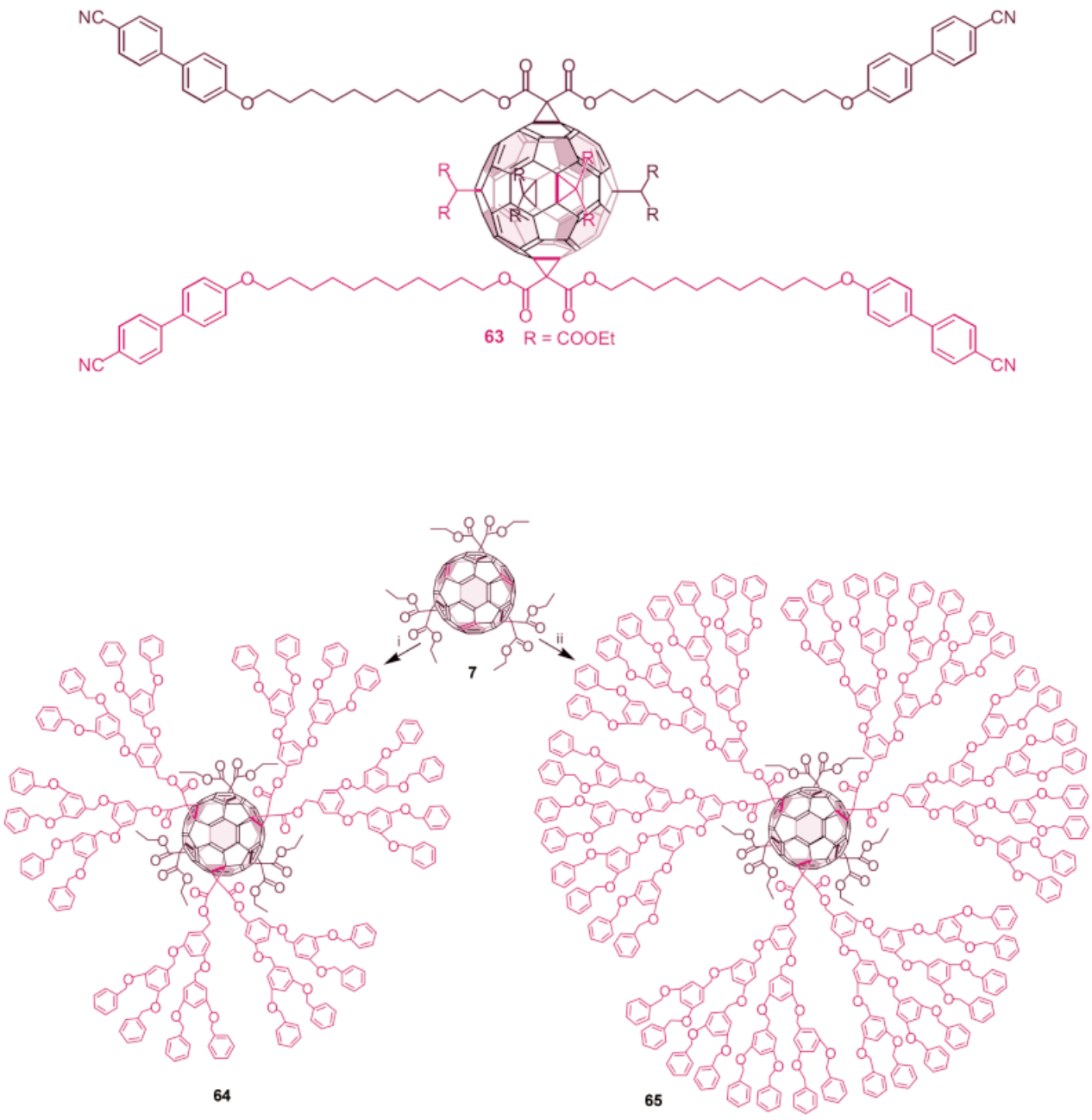
mixed tetrakisadduct **59** in 42% overall yield.[38] Transesterification yielded the octakis(ethyl ester) **60**, with two reactive [6,6] bonds at the poles. Addition of TMS-protected



Scheme 14. Topochemically controlled solid-state synthesis of bisadduct **56** and subsequent cyclopropanation to give [2:4] hexakisadduct **57**;[26,35] (i: 180 °C, 10 min; 40 equiv. ethyl bromomalonate **3**, 40 equiv. DBU)



Scheme 15. Tether-directed remote functionalization leading to tetraethynylated [2:4] hexakisadduct **62**;[2c,37] (i: O_2, hv, PhCl; ii: PPh_3, PhCl; iii: TosOH, ethyl acetylenedicarboxylate; iv: 3-bromo-1,5-bis(trimethylsilyl)-1,4-pentadiyne **61**)



Scheme 16. Synthesis of racemic second (G2) and third (G3) generation dendrimer [3:3] hexakisadducts **64** and **65** by nucleophilic cyclopropanation of **7**;[29] (i: DMA, $CHBr(COOG2)_2$, DBU, toluene, 2 d, room temp.; ii: $CHBr(COOG3)_2$, DBU, toluene, 2 d, room temp.)

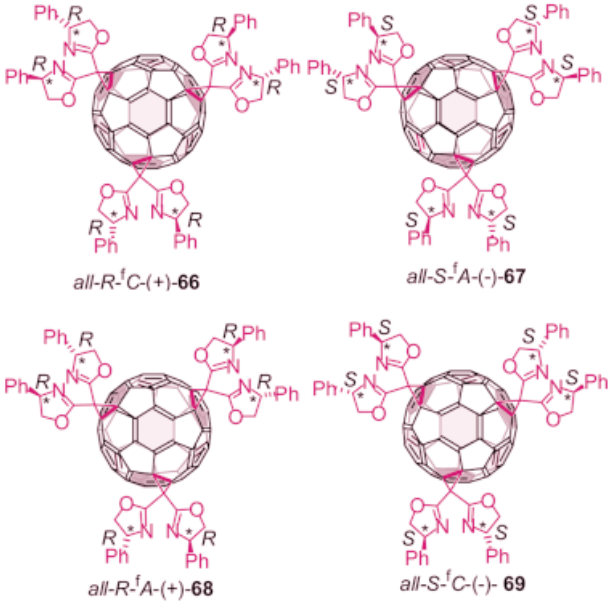
dialkynyl bromide **61** and subsequent deprotection of the product afforded tetraethynylated hexakisadduct **62**: [2c,37] a useful building block for further molecular nanoscaffolding.

The same tetrakisadduct **60** served as starting material for the synthesis of [4:2] hexakisadduct **63**.[39] Samples of **63** obtained by slow crystallization gave a nematic mesophase on first heating. After isotropization, no mesogenic behaviour could any longer be detected.[39]

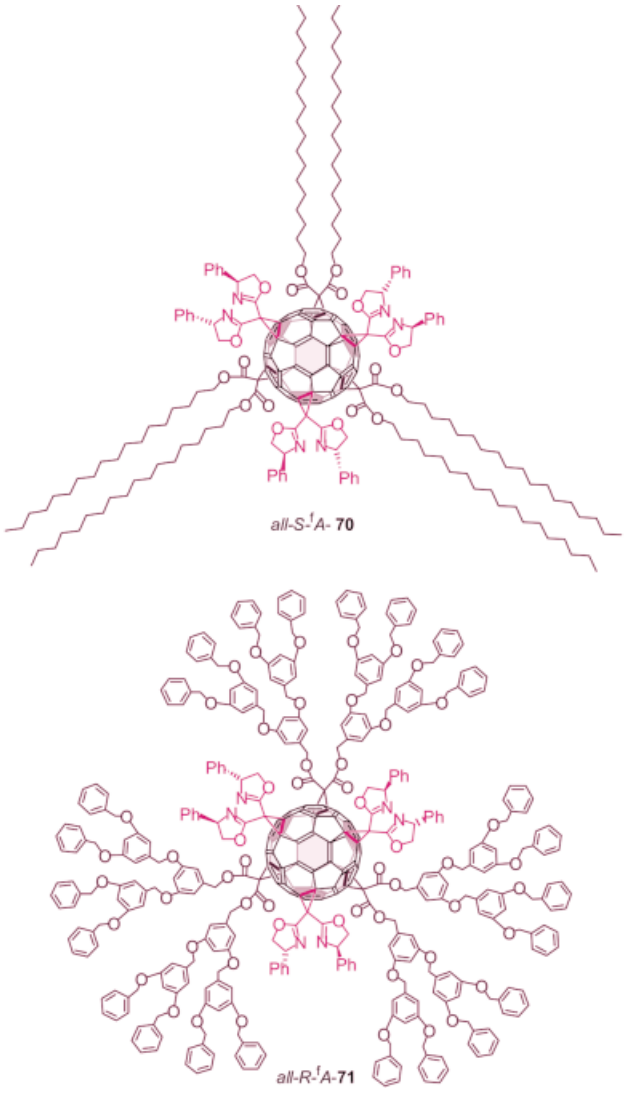
Mixed [3:3] Hexakisadducts

The synthesis of mixed [3:3] hexakisadducts of *type I* (Figure 2) requires trisadduct precursors with an *e,e,e*-addition pattern. As starting material for the synthesis of dendritic [3:3] adducts, we used the C_3-symmetrical trismalonate **7**.[3] For the completion of the octahedral addition pattern, DMA template-mediated cyclopropanation of **7** with the se-

cond and third generation bromomalonates $BrCH(COOG2)_2$ and $BrCH(COOG3)_2$ gave the mixed [3:3] dendrimers $C_{66}(COOEt)_6(COOG2)_6$ **64** and $C_{66}(COOEt)_6(COOG3)_6$ **65** in 44 and 28% yield, respectively (Scheme 16). Both chiral compounds have C_3 symmetry and were obtained as racemic mixtures from the racemic starting trisadduct **7**.[29]



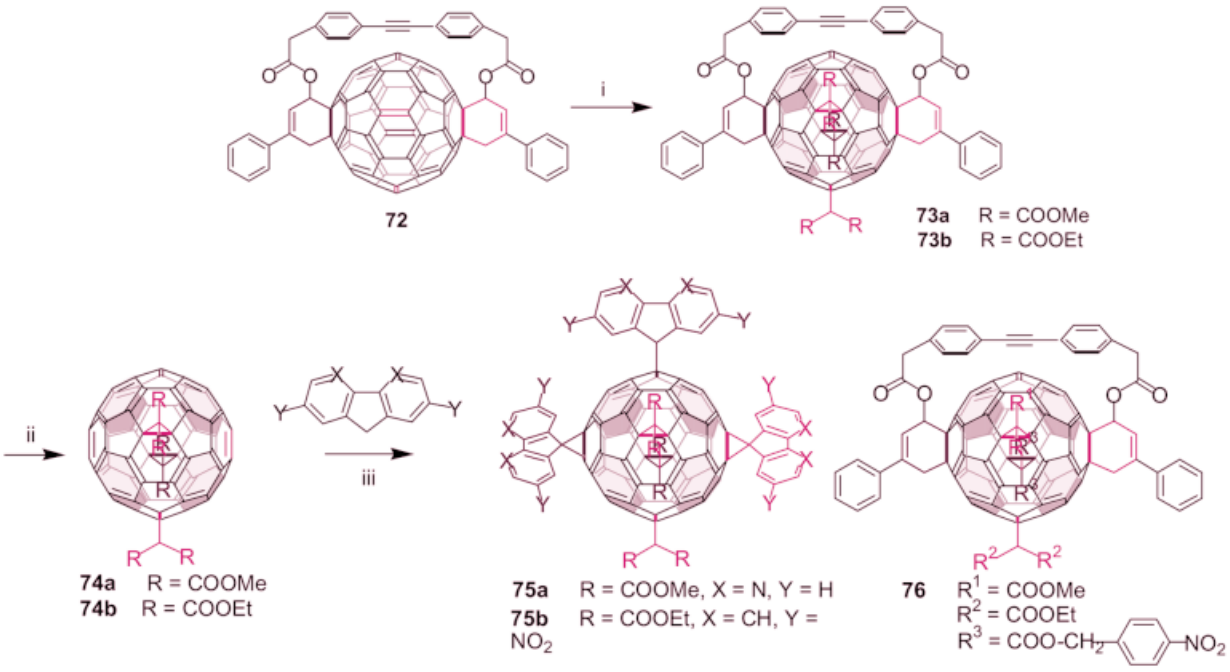
The synthesis of enantiomerically pure [3:3] hexakisadducts with an inherently chiral C_3-symmetrical addition pattern was achieved with tris[bis(4-phenyl-2-oxazolinemethano)] adducts *all-R-*^{f}*C*-(+)-**66**, *all-S-*^{f}*A*-(−)-**67**, *all-R-*^{f}*A*-(+)-**68** and *all-S-*^{f}*C*-(−)-**69**[5] (^fC = fullerene *C*lockwise, ^fA = fullerene *A*nticlockwise)[40] as precursor adducts of known absolute configurations. The adduct pairs **66** and **67**, and **68** and **69**, respectively, represent pairs of enantiomers. Dendritic second generation 3,5-dihydroxybenzylic bromomalonate[5] or lipophilic dioctadecyl bromomalonate[14] were used to complete the octahedral addition pattern. Examples of corresponding products are the *dendrizyme* **70** and the *lipofullerene* **71**.[6]



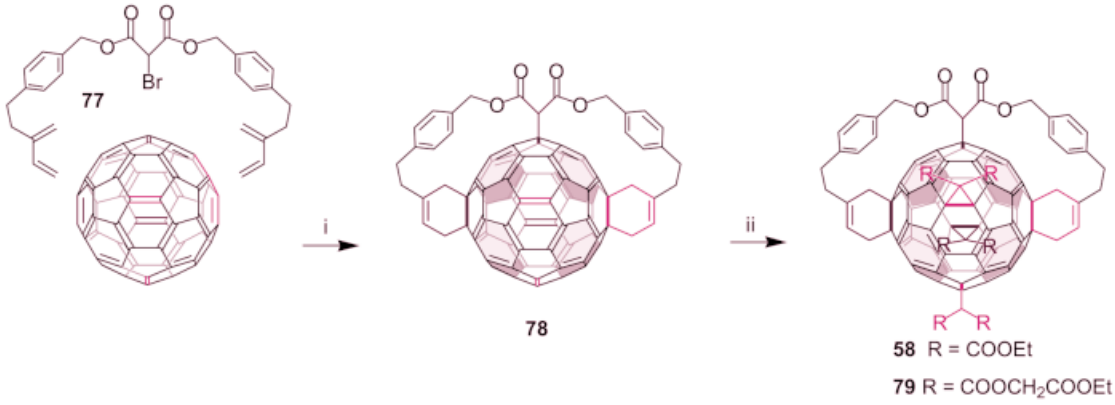
Access to [3:3] hexakisadducts of *type II* was achieved by Rubin and co-workers. With their synthesis of the tethered intermediate **72**, they developed an efficient method for a *trans*-1 functionalization of C_{60} (Scheme 16).[41] The *trans*-1 bisadduct **72** constitutes a strategically protected building block for the construction of octahedral systems. In **72**, thanks to the shielding engendered by the tether, only three of the four reactive *e*-positions are accessible for further addition reactions. As a consequence, treatment with dimethyl or diethyl malonate, under in situ bromination conditions (CBr_4 and DBU), gave mixed pentakisadducts **73a** and **73b**, respectively. The subsequent removal of the tether was achieved by an elimination/Diels−Alder/*retro*-Diels−Alder sequence. The resulting C_{2v}-symmetric trisadducts **74a** and **74b** both underwent highly regioselective threefold addition reactions with 4,5-diazafluorene or 2,7-dinitrofluorene, leading to the mixed [3:3] hexakisadducts **75a** and **75b** in 50% and 89% yield, respectively (Scheme 17).[41]

Thanks to the *trans*-1 regiochemistry of tethered bisadduct **72** and the ensuing single protected *e*′′-position, it is possible to address each of the three remaining *e*-positions exclusively, in sequential manner (*e*′, *e*′′, and finally *e*′), thus priming this synthesis method for complete differentiation between octahedral addition sites.[41]

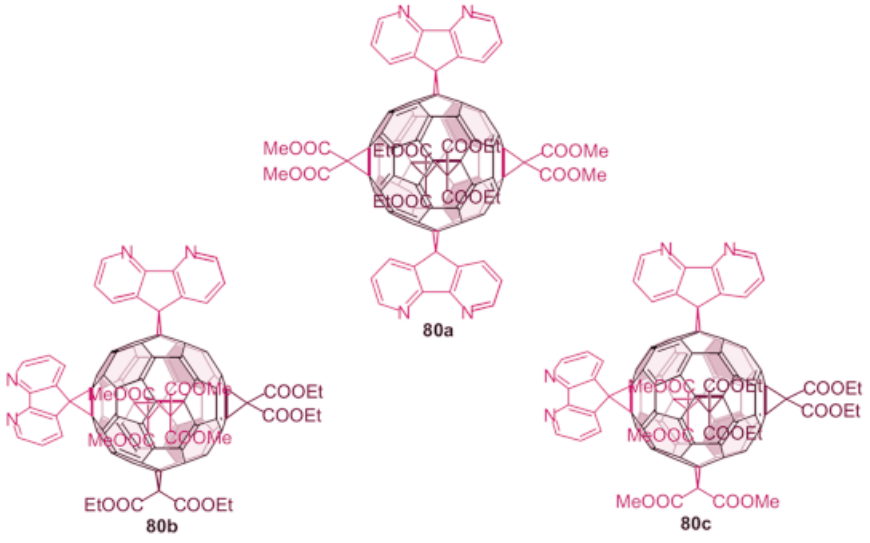
This synthesis technique represents an elegant means to embellish C_{60} with a large number of different addend types, giving access to multiple fullerene adducts with stereochemically defined geometry. This was demonstrated by the preparation of the [1:1:1:2] pentakisadducts **76**, incorporating three different malonates: methyl, ethyl and *p*-nitrobenzyl, respectively. These represent an important building block for possible future hexakisadducts with four different addends at octahedral sites.[41]



Scheme 17. Formation of the [3:3] hexakisadducts **75a** and **75b** and the [1:1:1:2] mixed pentakisadduct **76** exploiting tether *trans*-1 regiochemistry and fully addressable octahedral addition sites;[41] (i: methyl and ethyl malonate, respectively, CBr_4, DBU; ii: TosOH, DMAD, toluene, 110 °C; iii: fluorene derivative, CBr_4, DBU)



Scheme 18. Tether-mediated synthesis of [1:2:3] hexakisadducts **58** and **79**;[36,42] (i: DBU, toluene, room temp., 12 h, reflux 16 h; ii: 10 equiv. diethyl bromomalonate **3**, 10 equiv. DBU (**58**) or bis(2-ethoxy-2-oxoethyl)bromomalonate, DBU)



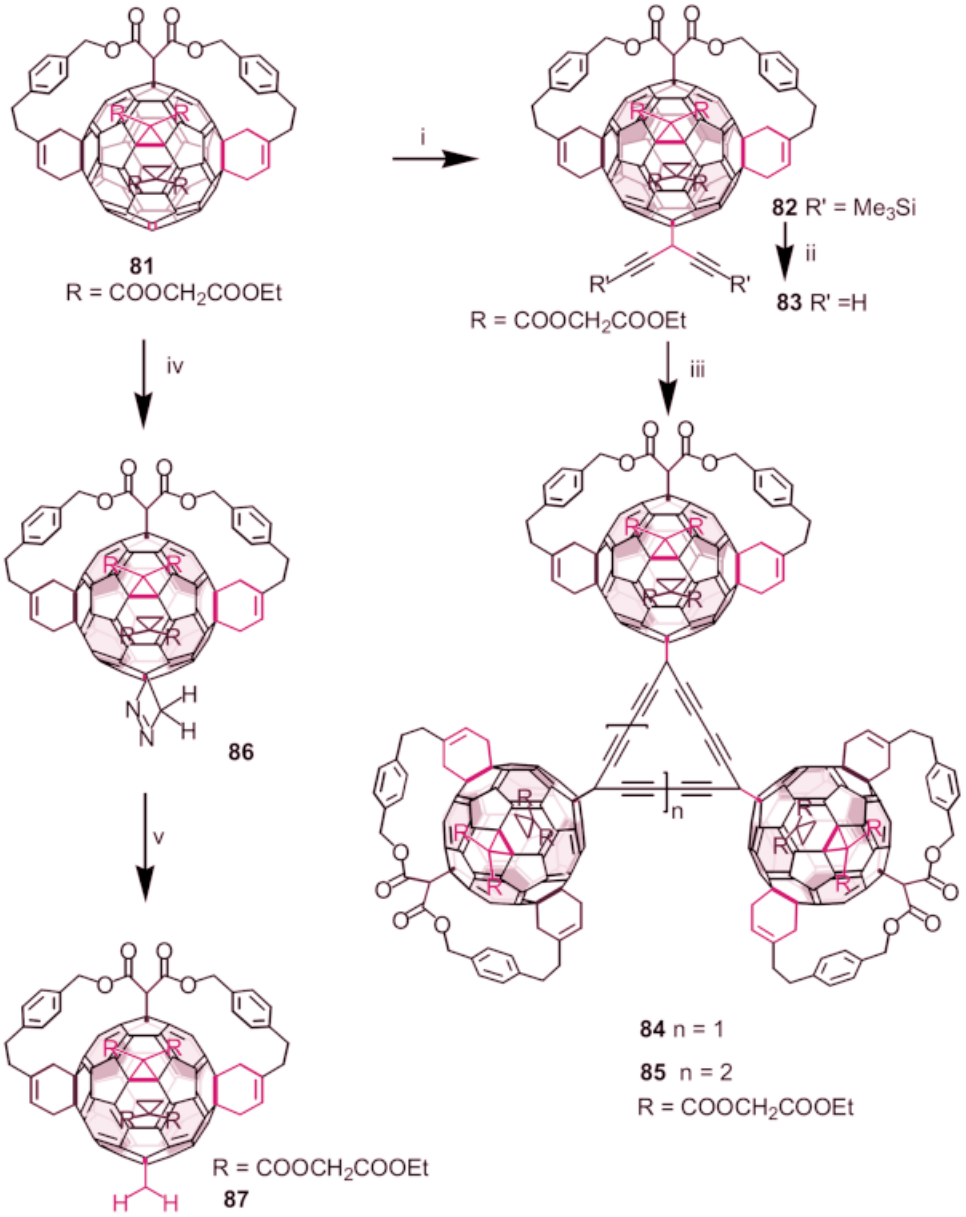
Mixed Hexakisadducts with Three Different Types of Addends

Mixed [1:2:3] Hexakisadducts

Using their tether-directed remote functionalization method, Diederich et al. synthesized a large variety of mixed hexakisadducts with more than two types of addends.[2] The synthesis of the first example, the adduct **58**, has already been shown in Scheme 15.[36,42] The trisfunctional anchor-tether **77** was monoattached to C_{60} by means of a nucleophilic cyclopropanation reaction. Subsequent Diels–Alder additions at the two *e*'-sites yielded the trisadduct **78** with complete regioselectivity. Cyclopropanation of **78** with 10 equivalents of bromomalonate gave rise to the formation of the C_{2v} symmetrical, bright yellow [1:2:3] hexakisadduct **58** (Scheme 18) in 73% yield.[36,42] A similar hexakisadduct **79** was obtained by a double cyclopropanation of **78** with bis(2-ethoxy-2-oxoethyl) bromomalonate to give a mixture of two pentaadducts, which after a final addition of two more equivalents of bromomalonate in the presence of DBU yielded **79**.[42]

Mixed [2:2:2] Hexakisadducts

Following their initial studies,[41] Rubin and co-workers consequently succeeded in the synthesis of a complete "library" of all-*e* C_{60} [2:2:2] hexakisadducts with three pairs of



Scheme 19. Tether-mediated synthesis of trimer C_{180} and tetramer C_{240} hexakisadducts **84** and **85**[42,44] and [1:1:2:2] hexakisadduct **87**;[45] (i: 10 equiv. 3-bromo-1,5-bis(trimethylsilyl)-1,4-pentadiyne **61**, 10 equiv. DBU; ii: $Bu_2NF(SiO_2)$; iii: 200 equiv. $Cu(OAc)_2$, molecular sieves 4A; iv: 60 equiv. CH_2N_2; v: hv)

addends in octahedral sites.[43] Using a "mer-3+3" regiocontrol strategy, involving regiochemically distinct cyclopropanations of *trans*-1 tethered bisadduct **72**, the authors prepared four regioisomeric trismalonates, each with two different ester moieties. This represented a fine-tuning of electronic and steric effects on the surface of C_{60}, enabling consequent, separate addition of further addends. Variation of addition sequences, as well as of the choice of the corresponding addends, via [2:2] mixed tetraadducts and [1:2:2] mixed pentaadducts, respectively, allowed the authors to obtain seven out of the eight possible regioisomeric [2:2:2] mixed hexakisadducts, such as, for example, **80a−c**.[43]

Mixed Hexakisadducts with Four Different Types of Addends

For the synthesis of mixed adducts with four different types of addends, Diederich and co-workers used pentakisadducts **81**, obtained by stepwise addition of bis(2-ethyl-2-oxoethyl) bromomalonate to starting material **78**.[42,44] Thesubsequent addition of dialkynyl bromide **61** to the re maining octahedral double bond occurred readily in DMSO in the presence of DBU, and hexakisadduct **82** was obtained in 88% yield. Starting from the bis-deprotected **83**, Eglington-Glaser macrolactonization afforded trimeric **84** and tetrameric **85** as stable, soluble nanoscaffolds (Scheme 19).[42,44] Compounds **84** and **85** are members of a new class of fullerene-acetylene hybrid carbon allotropes. Treatment of pentakisadduct **81** with diazomethane gave rise to the formation of pyrazolofullerene hexakisadduct **86**. When the latter was photolysed, one of the nitrogen extrusion products was the bright yellow methanofullerene **87** (Scheme 19).[45]

Acknowledgments

This work was supported by Aventis (Hoechst AG, Frankfurt), by the Deutsche Forschungsgemeinschaft DFG, the Volkswagen-Stiftung, the Bundesministerium für Bildung und Forschung (BMBF), and by the Fonds der Chemischen Industrie.

[1] [1a] A. Hirsch, *The Chemistry of the Fullerenes*, Thieme, New York **1994**. – [1b] A. Hirsch, *Synthesis* **1995**, 895−913. – [1c] A. Hirsch, *Top. Curr. Chem.*, **1998**, *199*, 1. – [1d] A. Hirsch, B. Nuber, *Acc. Chem. Res.* **1999**, *32*, 795−804.

[2] [2a] F. Diederich, C. Thilgen, *Science* **1996**, *271*, 317−323. – [2b] F. Diederich, *Pure Appl. Chem.* **1997**, *69*, 395−400. – [2c] F. Diederich, R. Kessinger, *Acc. Chem. Res.* **1999**, *32*, 537−545. – [2d] F. Diederich, R. Kessinger, in *Templated Organic Synthesis* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH Verlag, Weinheim, **2000**, 189−218. – [2e] F. Diederich, M. Gomez-Lopez, *Chem. Soc. Rev.* **1999**, *28*, 263−277. – [2f] M. Prato, M. Maggini, *Acc. Chem. Res.* **1998**, *31*, 519−526.

[3] A. Hirsch, I. Lamparth, H. R. Karfunkel, *Angew. Chem.* **1994**, *106*, 453−455; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 437−438.

[4] F. Diederich, C. Thilgen, A. Herrmann, *Nachr. Chem. Techn. Lab.* **1996**, *44*, 9.

[5] F. Djojo, A. Hirsch, *Chem. Eur. J.* **1998**, *4*, 344−356.

[6] F. Djojo, E. Ravanelli, A. Hirsch, O. Vostrowsky, *Eur. J. Org. Chem.* **2000**, 1051−1059.

[7] P. J. Fagan, J. C. Calabrese, B. Malone, *J. Am. Chem. Soc.* **1991**, *113*, 9408−9409.

[8] P. J. Fagan, J. C. Calabrese, B. Malone, in *Fullerenes: Synthesis, Properties, and Chemistry of Large Carbons Clusters*; (Eds.: G. S. Hammond, V. J. Kuck), American Chemical Society Symposium Series *481*, **1992**, p. 177.

[9] P. J. Fagan, J. C. Calabrese, B. Malone, *Acc. Chem. Res.* **1992**, *25*, 134−142.

[10] [10a] A. Hirsch, I. Lamparth, T. Grösser, H. R. Karfunkel, *J. Am. Chem. Soc.* **1994**, *116*, 9385−9386. – [10b] A. Hirsch, I. Lamparth, T. Grösser, M. Prato, V. Lucchini, F. Wudl, *Regioselective Multiple Additions to Buckminsterfullerene* (Ed.: W. Andreoni), in *The Chemical Physics of Fullerenes 10 (and 5) Years Later*, Kluwer Academic Publishers, Netherlands, **1996**, 267−283.

[11] I. Lamparth, C. Maichle-Mössmer, A. Hirsch, *Angew. Chem.* **1995**, *107*, 1755−1757; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1607−1609.

[12] B. Kräutler, J. Maynollo, *Angew. Chem.* **1995**, *107*, 69−71; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 87−89.

[13] I. Lamparth, A. Herzog, A. Hirsch, *Tetrahedron* **1996**, *52*, 5065−5075.

[14] X. Camps, A. Hirsch, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1595−1596.

[15] M. Hetzer, S. Bayerl, X. Camps, O. Vostrowsky, A. Hirsch, T.M. Bayerl, *Adv. Mater.* **1997**, *9*, 913−917.

[16] M. Hetzer, T. Gutberlet, M. F. Brown, X. Camps, O. Vostrowsky, H. Schönberger, A. Hirsch, T. M. Bayerl, *J. Phys. Chem. A* **1999**, *103*, 637−642.

[17] M. Hetzer, H. Clausen-Schaumann, S. Bayerl, T. M. Bayerl, X. Camps, O. Vostrowsky, A. Hirsch, *Angew. Chem.* **1999**, *111*, 2103−2106; *Angew. Chem. Int. Ed.* **1999**, *38*, 1962−1965.

[18] H. Schönberger, Ph. D. Dissertation, Universität Erlangen-Nürnberg, **2000**.

[19] X. Camps, H. Schönberger, A. Hirsch, *Chem. Eur. J.* **1997**, *3*, 561−567.

[20] X. Camps, E. Dietel, A. Hirsch, S. Pyo, L. Echegoyen, S. Hackbarth, B. Röder, *Chem. Eur. J.* **1999**, *5*, 2362−2373.

[21] T. Chuard, R. Deschenaux, A. Hirsch, H. Schönberger, *Chem. Commun.* **1999**, 2103−2104.

[22] M. Brettreich, Ph. D. Dissertation, Universität Erlangen-Nürnberg, **2000**.

[23] T. Da Ros, M. Prato, *Chem. Commun.* **1998**, 663−669.

[24] G. Schick, M. Levitus, L. Kvetko, B. A. Johnson, I. Lamparth, M. Lunkwitz, B. Ma, S. I. Khan, M. A. Garcia-Garibay, Y. Rubin, *J. Am. Chem. Soc.* **1999**, *121*, 3246−3247.

[25] K. Hutchison, J. Gao, G. Schick, Y. Rubin, F. Wudl, *J. Am. Chem. Soc.* **1999**, *121*, 5611−5612.

[26] B. Kräutler, T. Müller, J. Maynollo, K. Gruber, C. Kratky, P. Ochsenbein, D. Schwarzenbach, H.-B. Bürgi, *Angew. Chem.* **1996**, *108*, 1294−1296; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1204−1206.

[27] M. Brettreich, S. Burghardt, C. Böttcher, S. Bayerl, T. Bayerl, A. Hirsch, *Angew. Chem.* **2000**, *112*, 1915−1918; *Angew. Chem. Int. Ed.* **2000**, *39*, 1845−1848.

[28] M. Braun, X. Camps, O. Vostrowsky, A. Hirsch, E. Endreß, T. M. Bayerl, O. Birkert, G. Gauglitz, *Eur. J. Org. Chem.* **2000**, 1173−1181.

[29] A. Herzog, A. Hirsch, O. Vostrowsky, *Eur. J. Org. Chem.* **2000**, 171−180.

[30] P. Timmerman, L. E. Witschel, F. Diederich, C. Boudon, J.-P. Gisselbrecht, M. Gross, *Helv. Chim. Acta* **1996**, *79*, 6−20.

[31] T. Habicher, J.-F. Nierengarten, V. Gramlich, F. Diederich, *Angew. Chem* **1998**, *110*, 2019−2022; *Angew. Chem. Int. Ed.* **1998**, *37*, 1916−1919.

[32] *Dendritic Molecules* (Eds.: G. R. Newkome, C. N. Moorefield, F. Vögtle), VCH Weinheim, New York, Basel, Cambridge, Tokyo **1996**.

[33] A.P. Maierhofer, M. Brettreich, O. Vostrowsky, A. Hirsch, S. Langridge, T. Bayerl, *Langmuir* **2000**, in press.

[34] M. Scheloske, E. Dietel, A. Hirsch, **2000**, in preparation.

[35] R. Schwenninger, T. Müller, B. Kräutler, *J. Am. Chem. Soc.* **1997**, *119*, 9317−9318.

[36] L. Isaacs, R. F. Haldimann, F. Diederich, *Angew. Chem.* **1994**,

106, 2434−2437; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2339−2342.
[37] F. Cardullo, L. Isaacs, F. Diederich, J.-P. Gisselbrecht, C. Boudon, M. Gross, *Chem. Commun.* **1996**, 797−799.
[38] F. Cardullo, P. Seiler, L. Isaacs, J.-F. Nierengarten, R. F. Haldimann, F. Diederich, T. Mordasini-Denti, W. Thiel, C. Boudon, J.-P. Gisselbrecht, M. Gross, *Helv. Chim. Acta* **1997**, *80*, 343−371.
[39] N. Tirelli, F. Cardullo, T. Habicher, U. W. Suter, F. Diederich, *J. Chem. Soc., Perkin Trans. 2* **2000**,193−198.
[40] C. Thilgen, A. Herrmann, F. Diederich, *Helv. Chim. Acta* **1997**, *80*, 183−199.
[41] W. Quian, Y. Rubin, *Angew. Chem.* **1999**, *111*, 2504−2508; *Angew. Chem. Int. Ed.* **1999**, *38*, 2356−2360.
[42] L. Isaacs, F. Diederich, R. F. Haldimann, *Helv. Chim. Acta* **1997**, *80*, 317−342.
[43] W. Quian, Y. Rubin, *Angew. Chem.* **2000**, *112*, in press; *Angew. Chem. Int. Ed.* **2000**, in press.
[44] L. Isaacs, P. Seiler, F. Diederich, *Angew. Chem.* **1995**, *107*, 1636−1639; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1466−1469.
[45] R. F. Haldimann, F.-G. Klärner, F. Diederich, *Chem. Commun.* **1997**, 237−238.

Received May 15, 2000
[O00235]