

Templated Regioselective and Stereoselective Synthesis in Fullerene Chemistry

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Introduction

The covalent functionalization of buckminsterfullerene, C_{60} , has developed dramatically over the past eight years, and a great diversity of synthetic protocols for the formation of monoadducts are becoming available.¹ In contrast, the sequential multiple functionalization of the carbon sphere in most cases is problematic since it leads to regioisomeric product mixtures which require tedious chromatographic separation. Some multiple addition patterns do not form at all in sequential reactions. Regioisomerically pure higher adducts of C_{60} are usually only obtained in additions of transition metal complexes² and radical halogenations;³ these reactions either occur under thermodynamic control or lead to the precipitation of the least soluble derivative.⁴ In 1994, we proposed a more general approach to the regioselective formation of multiple adducts of C_{60} by tether-directed remote functionalization.⁵ A similar strategy had been previously developed by Breslow and co-workers for the selective functionalization of steroids and long-chain alkanes.⁶ Templated synthesis is rapidly becoming the method of choice for regio- and stereoselective multiple functionalization of C_{60} . This Account describes how covalent templates, such as reversibly removable addends and tethers,⁷ are applied to provide access to a great diversity of three-dimensionally functionalized fullerene building blocks. With these derivatives in hand, changes in the unique properties of parent C_{60} (such as facile reversible multiple electrochemical reducibility⁸ and efficient singlet oxygen sensitization⁹) with increasing degree of functionalization and concomitant reduction of the fullerene chromophore can be

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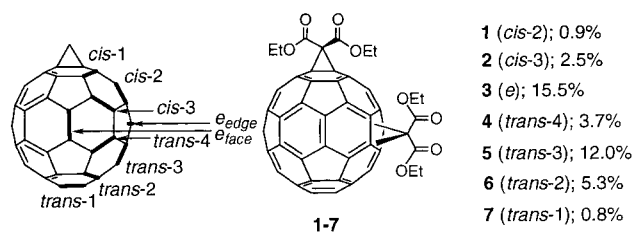


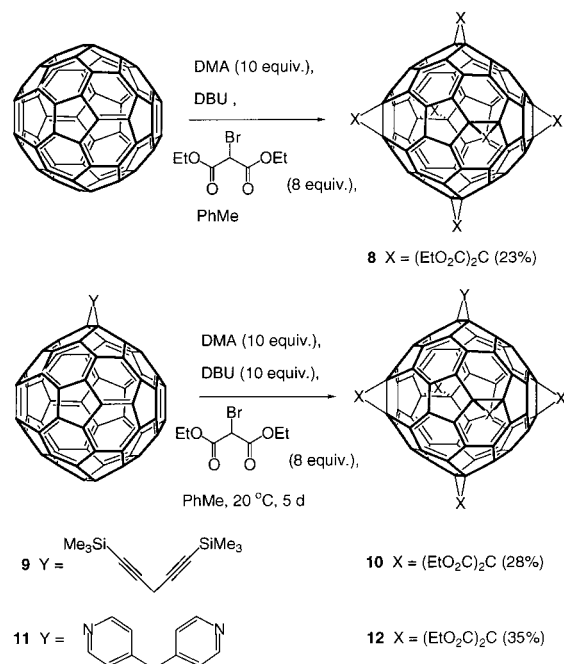
FIGURE 1. Position notation for bisadducts of C_{60} and products isolated from the second Bingel addition (diethyl 2-bromomalonate, NaH, toluene, room temperature (rt)) to bis(diethoxycarbonyl)methano[60]fullerene [$C_{61}(\text{COOEt})_2$].¹³

investigated in great detail. Higher adducts of C_{60} are increasingly finding application in the construction of supramolecular advanced materials;¹⁰ furthermore, they have been of substantial interest in the exploration of the different origins of fullerene chirality.¹¹

Synthesis of Higher Adducts of C_{60} Using Anthracene as a Reversible Covalent Template

The problem of regioisomeric product formation in nucleophilic additions to C_{60} is best illustrated by the sequential double Bingel cyclopropanation¹² with diethyl 2-bromomalonate in the presence of base. Of the eight possible bisadducts, named by Hirsch et al. as *cis*-1–3, *e*_{face} and *e*_{edge} (these two bisadducts are identical if the two addends are identical), and *trans*-1–4¹³ (Figure 1), seven (1–7) were obtained in various amounts. Upon moving to higher adducts, the regioselectivity of the additions becomes remarkably enhanced. Thus, the introduction of a third addend in the Bingel reaction occurs preferentially (40%) in the equatorial (*e*) position, and starting from the purified *e,e,e* trisadduct, an amazing succession of stepwise *e* additions, with regard to the previous addends, leads in high yield to hexakisadduct **8** with a pseudo-octahedral, all-*e* addition pattern.¹⁴ Starting from C_{60} and **8** equiv of diethyl 2-bromomalonate/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), hexakisadduct **8** is directly obtained in 14% yield.¹⁵

The yield of **8**, starting from C_{60} , can be almost doubled and its workup and separation from other products greatly facilitated, if 1,9-dimethylantracene (DMA; 10 equiv) is used as a template which undergoes reversible Diels–Alder additions with the fullerene.¹⁵ After addition to the fullerene, the template directs diethyl malonate addends in the Bingel reaction regioselectively into *e* positions, ultimately yielding hexakisadduct **8** (23% yield) (Scheme 1).¹⁶ The templated activation of *e* 6–6 bonds (bonds between two six-membered rings) is also efficient starting from C_{60} monoadducts.¹⁵ Thus, the bis(alkynyl)methano-fullerene **9** reacted with diethyl 2-bromomalonate/DBU (8 equiv) and DMA (12 equiv) to provide hexakisadduct **10** in 28% yield.¹⁷ Without template, the yield was only 12% and the targeted product was contaminated with an inseparable impurity. Also, monoadduct **11** was transformed in 35% yield into hexakisadduct **12**,¹⁸ the precursor for the Pt(II)-directed self-assembly of a dinuclear cyclo-

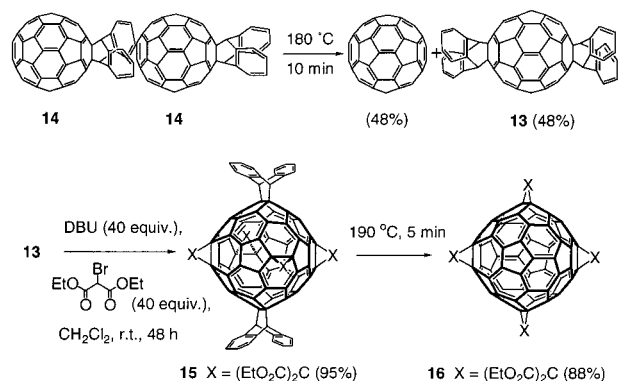
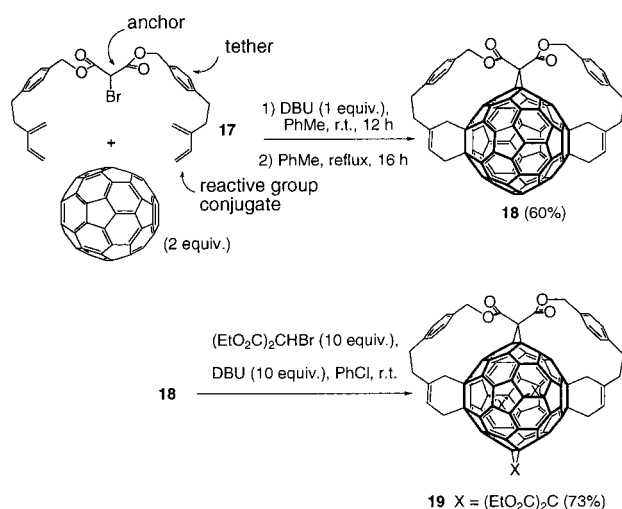
Scheme 1. Synthesis of Hexakisadducts of C₆₀, 8,¹⁵ 10,¹⁷ and 12,¹⁸ Using 1,9-Dimethylantracene (DMA) as Template


phane of the molecular-square type containing two appended fullerenes.

In the elegant preparation of *trans*-1 bisanthracene adduct **13** by Kräutler and co-workers, the crystal packing provided the molding effect characteristic of a template.¹⁹ Heating a sample of crystalline monoadduct **14** at 180 °C for 10 min afforded 48% each of C₆₀ and bisadduct **13**, resulting from a topochemically controlled, intermolecular anthracene-transfer reaction (Scheme 2). The two anthracene addends in **13** were subsequently used to direct four malonate addends regioselectively into the *e* positions, giving hexakisadduct **15**, and thermal removal of the anthracene templates provided tetrakisadduct **16** with all four addends aligned along an equatorial belt on the carbon sphere.^{20,21}

Higher Adducts of C₆₀ by Tether-Directed Remote Functionalization

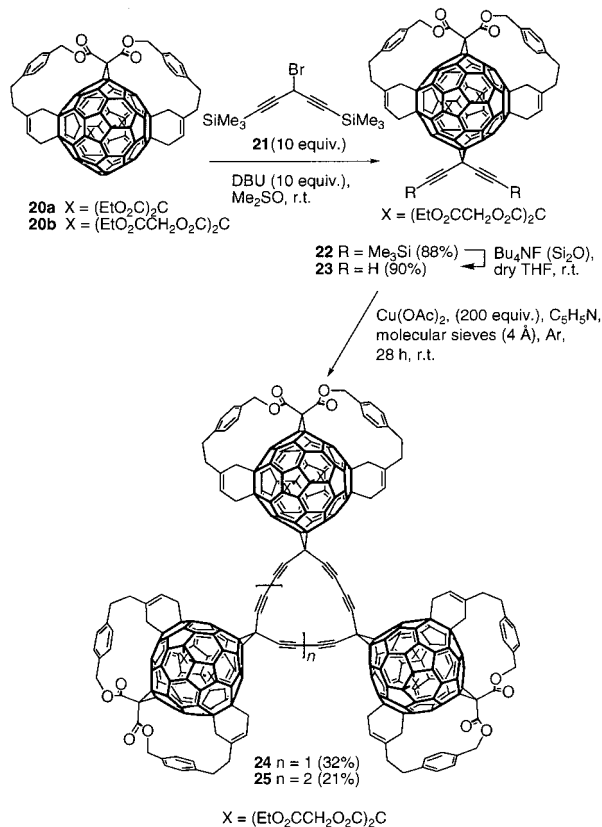
Tether-directed remote functionalization of C₆₀ allows construction of fullerene derivatives with addition patterns that are difficult to obtain by thermodynamically or kinetically controlled reactions with free untethered reagents. Anchor-tether-reactive group conjugates such as **17** were designed by semiempirical PM3 calculations using as selection criterion the relative heat of formation of the theoretically possible fullerene adducts.^{5,22,23} As predicted, conjugate **17** underwent, after attachment through a Bingel reaction to C₆₀, Diels–Alder additions at the two *e* positions on opposite sides of the carbon sphere, yielding trisadduct **18** in 60% yield with complete regioselectivity (Scheme 3). Reaction of **18** with a large excess of diethyl 2-bromomalonate and DBU in toluene gave by sequential *e* additions in 73% yield the yellow hexakisadduct **19**, in

Scheme 2. Topochemical Solid-State Synthesis of Bisadduct 13¹⁹ and Templated Synthesis of Tetrakisadduct 16 Using Anthracene as Reversible Covalent Template²⁰

Scheme 3. Preparation of Trisadduct 18 by Tether-directed Remote Functionalization and Subsequent Sequential *e* Attacks Generating Octahedral Hexakisadduct 19^{5,22}


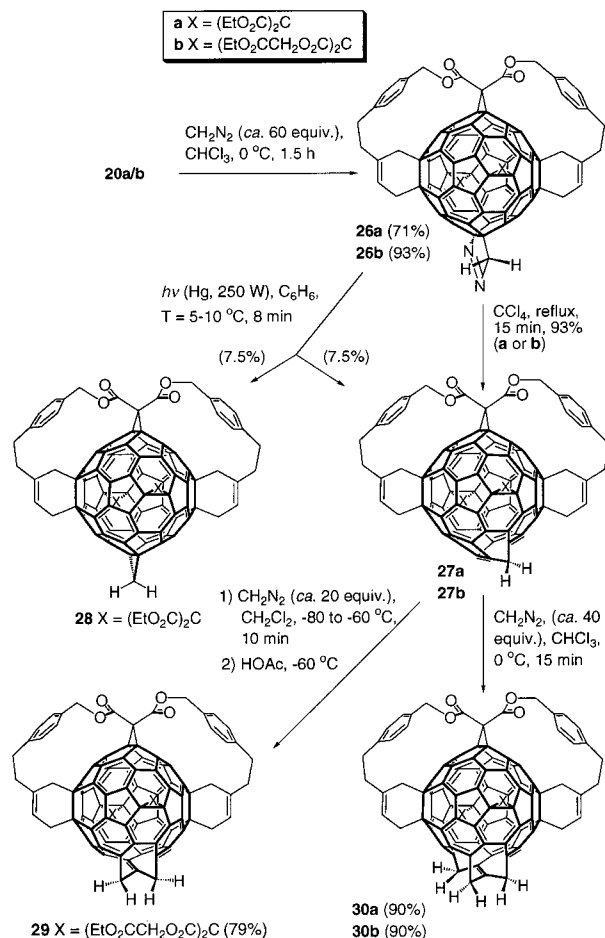
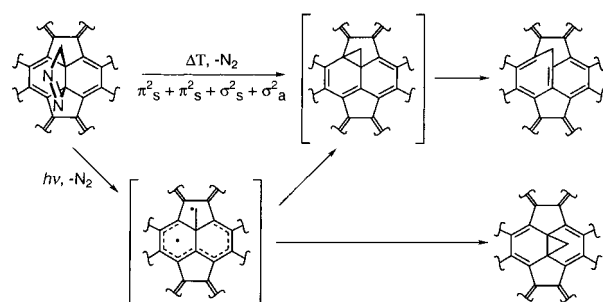
which the fullerene π -chromophore is reduced to a benzenoid cubic cyclophane substructure.^{24,25}

Stepwise malonate additions starting from **18** also provided novel tetrakis- and pentakisadducts (**20a/b**), with the reactivity of the carbon sphere in the latter being reduced to one remaining *e* 6–6 bond. Addition of dialkynyl bromide **21** to this bond in **20b** occurred readily in Me₂SO in the presence of DBU, and hexakisadduct **22** was obtained in 88% yield (Scheme 4).^{22,24} Starting from bis-deprotected **23**, Eglinton–Glaser macrocyclization afforded in a combined yield of 53% trimeric **24** and tetrameric **25** as stable, soluble carbon-rich nanoscaffolds. Compounds **24** (MW = 5317) and **25** (MW = 7086) are solubilized derivatives of C₁₉₅ and C₂₆₀, two members of a new class of fullerene–acetylene hybrid carbon allotropes with the general formula C_{n(60+5)}. Their matrix-assisted laser-desorption time-of-flight (MALDI-TOF) mass spectra showed remarkable fragmentation patterns: sequential loss of fullerene spheres led to the formation of ions corresponding to monofullerene adducts of the cyclocarbons²⁶ cyclo-C₁₅ and cyclo-C₂₀, respectively.

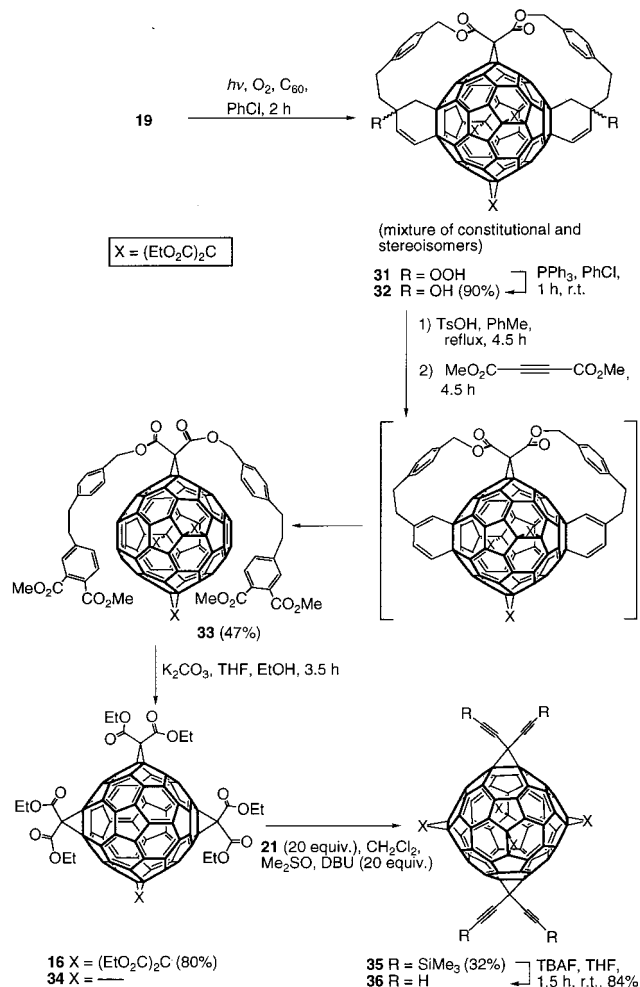
Repeated treatment of pentakisadducts **20a/b** with diazomethane provided—via hexakisadducts **27a/b**—with

Scheme 4. Synthesis of the Fullerene-appended Macrocycles **24** and **25**, Solubilized Derivatives of C_{195} and C_{260} , Respectively^{22,24}


high regioselectivity and excellent yields the novel heptakisadduct (**29**) and octakisadducts **30a/b** in which methano groups bridge the open junctions between a six- and a five-membered ring (6–5-open methanofullerenes) (Scheme 5).²⁷ Interestingly, the intermediate pyrazolines **26a/b**²⁸ could only be isolated during the formation to hexakisadducts **27a/b**, but not during the subsequent conversions in which N₂ extrusion occurred quickly even at low temperatures. The products obtained by both thermolysis and photolysis of pyrazoline **26a** are similar to those isolated in the addition of diazomethane to C₆₀ followed by N₂ extrusion:^{28,29} the thermal process exclusively provided the 6–5-open derivative **27a**, whereas photolysis gave a 1:1 mixture of 6–5-open (**27a**) and 6–6-closed (**28**) methanofullerenes.³⁰ On the basis of analogy to the product distribution previously observed in the N₂-elimination from diazoalkane–toluene adducts,³¹ we proposed that thermolysis of **26a** provides in an orbital symmetry controlled [$\pi^2_s + \pi^2_s + \sigma^2_s + \sigma^2_a$] rearrangement an intermediate norcaradiene substructure which then ring-opens to the cycloheptatriene substructure in the 6–5-open methanofullerene (Scheme 6).^{27,32} In contrast, photolysis presumably proceeds via a diradical mechanism, leading to a mixture of **27a** and **28**. This mechanism also explains the formation of the higher adducts **29** and **30a/b**. It might also account for the analogous preference of azide adducts of C₆₀ to thermally form 6–5-open azafullerenes.³³ Recent high-level calculations provide strong support for the mechanism depicted in Scheme 6.³⁴

 Scheme 5. Regioselective Formation of Hexakisadducts to Octakisadducts by Addition of Diazomethane to Pentakisadducts **20a/b**, Followed by Dinitrogen Extrusion²⁷

 Scheme 6. Proposed Mechanism for the Thermal and Photochemical N₂ Extrusion from Diazomethane Adducts of Fullerenes (Shown Only in Part)²⁷


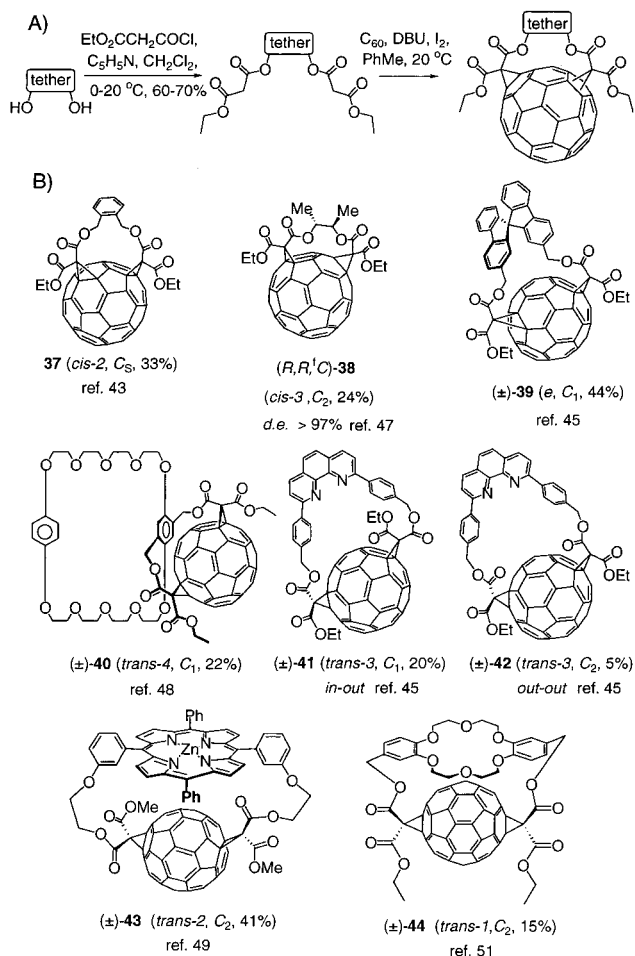
A tether-directed remote functionalization should only be called a template-directed reaction if the tether is removable. However, a direct removal of the *e*-directing cyclohexene rings together with the *p*-xylylene tethers in hexakisadduct **19** or pentakisadducts **20a/b** by retro-Diels–Alder reaction was not successful.³⁵ Therefore, an elegant, although less direct, procedure introduced by Rubin and co-workers³⁶ was applied. When a solution of **19** containing C₆₀ as ¹O₂ sensitizer was irradiated while a stream of O₂ was bubbled through, the ¹O₂ ene reaction at the two cyclohexene rings yielded a mixture of isomeric allylic hydroperoxides **31** with endocyclic double bonds

Scheme 7. Synthesis of the Tetraethynylated Hexakisadduct **36 via Tetrakisadduct **16**^{21,35,37} (TsOH = Toluene-4-sulfonic Acid)**


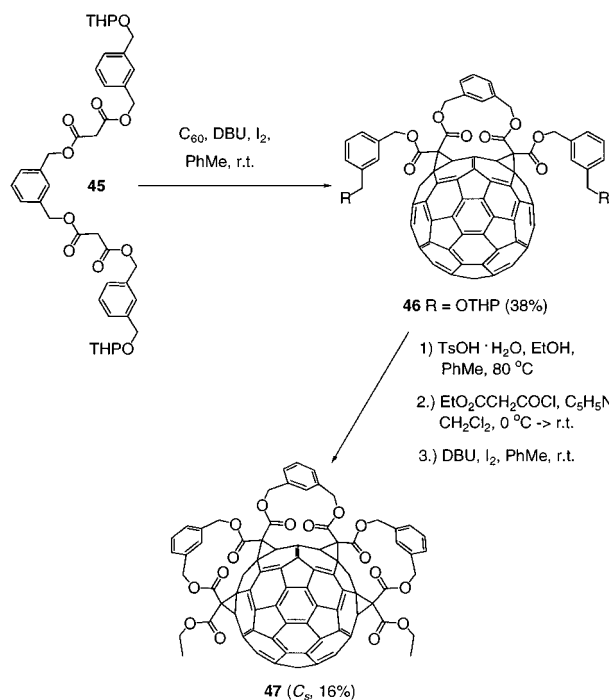
(Scheme 7).^{21,37} In situ reduction of **31** with PPh₃ gave a mixture of isomeric allylic alcohols **32**, which was subsequently heated in toluene together with toluene-4-sulfonic acid (TsOH) and dimethyl acetylenedicarboxylate (DMAD). Under these conditions, **32** was dehydrated to the corresponding bis(cyclohexa-1,3-diene) derivative, which, via a Diels–Alder retro-Diels–Alder sequence, afforded tetrakisadduct **33** in 42% overall yield starting from **19**. Transesterification yielded the octakis(ethyl ester) **16**, which was characterized by X-ray crystallography. By a similar sequence, trisadduct **34** was prepared starting from pentakisadduct **20b**.

Tetrakisadduct **16** contains two reactive 6–6 bonds at the pole activated by the four malonate addends in *e* positions at the equator. Thus, addition of 2 equiv of dialkynyl bromide **21** afforded hexakisadduct **35** and, after deprotection, tetrakisethynylated **36**, a useful building block for further molecular nanoscaffolding.³⁵

At the center of our interest in the preparation of all of these higher adducts was the exploration of how fullerene properties change with increasing reduction of the conjugated π -chromophore resulting from increasing functionalization. Thus, the physical properties and chemical reactivity of the multiple adducts were comprehensively

Scheme 8. (A) General Synthetic Protocol for the Efficient Regioselective and Stereoselective Preparation of Bis(cyclopropanated) [60]Fullerene Derivatives by Macrocyclization of C₆₀ via Double Bingel Addition^{43,45} and (B) Examples of Bisadducts Produced


investigated as a function of degree and pattern of addition and the nature of the addends.³⁷ Methods applied to these studies were UV/vis, IR, and NMR (¹H and ¹³C) spectroscopy, cyclic (CV) and steady-state (SSV) voltammetry,³⁸ calculations of LUMO energies and electron affinities, and chemical competition experiments. Furthermore, the endohedral ³He complexes of higher adducts such as **18**, **19**, and **20b** were prepared and the π -electron ring-current effects studied by ³He NMR.³⁹ Strong correlations and trends were revealed. In general, with increasing reduction in the conjugated fullerene π -chromophore, (i) the optical (HOMO–LUMO) gap in the UV/vis spectrum shifts to higher energy, (ii) the number of reversible (on the CV time scale) one-electron reductions decreases, and the first reduction potential becomes increasingly negative, (iii) the computed LUMO energy increases and the electron affinity decreases, (iv) the reactivity of the fullerene toward nucleophiles and carbenes or as dienophiles in cycloadditions decreases, and (v) the capacity for photosensitization of ¹O₂ formation decreases.⁴⁰ Fullerene properties are also affected by the nature of the addends. Thus, we found a strong difference between cyclopropane and cyclohexene fu-

Scheme 9. Preparation of Tetrakisadduct **47** by a Sequence of Two Bingel Macrocyclizations⁴⁵ (THP = 3,4,5,6-Tetrahydro-2H-pyran-2-yl)

sion: in general, all-cyclopropane-fused fullerenes exhibit a lower-energy optical gap, more reversible one-electron reductions at less negative potential, lower LUMO energies, and higher electrophilic reactivity than cyclohexene-fused derivatives. Apparently, cyclopropane fusion represents a smaller perturbation of the fullerene chromophore than cyclohexene fusion, and this effect is also observed in ³He NMR studies of endohedral ³He compounds.⁴¹ The smallest perturbation of the fullerene π -chromophore by multiple additions occurs when all-methano addends are introduced along an equatorial belt as in **16**.^{37,42} This is a useful guideline for the construction of highly functionalized fullerene derivatives designed to retain the properties of the parent carbon sphere.

The Bingel Macrocyclization

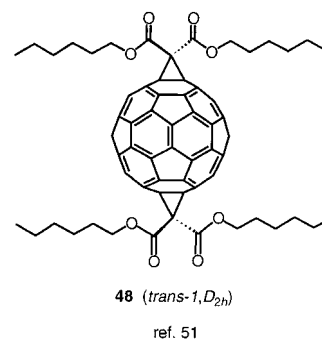
The macrocyclization between C₆₀ and bismalonate derivatives in a double Bingel reaction provides the most versatile and simple method for the preparation of covalent bisadducts of C₆₀ with high regio- and diastereoselectivity (Scheme 8). With the exception of *cis*-1, all possible bisaddition patterns (Figure 1) have been obtained by this tether-directed remote functionalization; selected examples (**37**–**44**) are presented in Scheme 8.^{43–45} As a general synthetic protocol, diols are transformed into bis(ethyl malonyl) derivatives and the one-pot reaction of C₆₀, bis(ethyl malonate), I₂ (to prepare the corresponding halomalonate in situ), and DBU in toluene at 20 °C generates the macrocyclic bisadducts in yields usually between 20% and 40% and high regio- and diastereoselectivity.

In theory, each macrocyclic regioisomer could form as a mixture of diastereoisomers, depending on how the

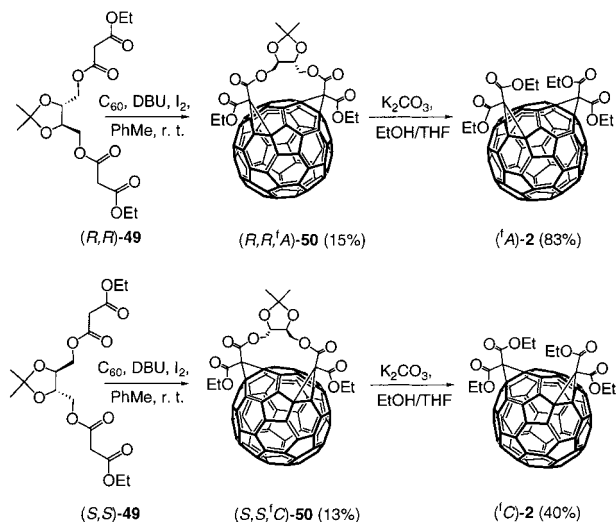
EtOCO residues at the two methano bridge C-atoms are oriented with respect to each other (*in-in*, *in-out*, and *out-out* stereoisomerism).⁴⁶ However, with the exception of the *in-out* isomer **41**, *out-out* stereoisomers have been obtained exclusively until now. The *out-out* geometry of *cis*-2 bisadduct **37** with an *o*-xylylene tether was proven by X-ray crystallography.⁴³

Higher adducts are also accessible in a regiospecific way. Thus, a clipping reaction starting from *cis*-2 bisadduct **46** (prepared by Bingel macrocyclization of **45**) yielded tetrakisadduct **47** with an all-*cis*-2 addition pattern along an equatorial belt (Scheme 9).⁴⁵ It is evident that, by a judicious combination of tethers, a rich variety of higher adducts of C₆₀ with original addition patterns should become accessible.⁵⁰

The tether in the bisadducts can be readily removed, making it a true template. Thus, transesterification of the fullerene crown ether conjugate (\pm)-**44** yielded the *D*_{2h}-symmetrical bisadduct **48** (34%),⁵¹ thereby providing a versatile entry into diverse molecular scaffolding using *trans*-1 bisadducts of C₆₀.⁵²



A sequence of a highly diastereoselective Bingel macrocyclization using a nonracemic tether, followed by removal of the tether via transesterification provided an enantioselective synthesis of optically active bisadducts in which the chirality results exclusively from the addition pattern.^{11,43,45} Starting from (*R,R*)-**49** and (*S,S*)-**49**, which were prepared from the corresponding optically pure diols, the two enantiomeric *cis*-3 bisadducts (*R,R*,^f*A*)-**50** and (*S,S*,^f*C*)-**50** were obtained with high diastereoselectivity (diastereoisomeric excess (de) > 97%) (Scheme 10). In each macrocyclization, two diastereoisomeric *out-out cis*-3 bisadducts are possible due to the chiral addition pattern; however, the high asymmetric induction by the optically active tether in the second intramolecular Bingel addition led to the formation of (*R,R*,^f*A*)-**50** and (*S,S*,^f*C*)-**50** only. The simple stereochemical descriptors ^f*C* and ^f*A* (*f* = fullerene, *C* = clockwise, *A* = anticlockwise) had been introduced to specify the configurations of chiral fullerenes and fullerene derivatives with a chiral functionalization pattern.^{11a} Similarly, the *cis*-3 adducts (*R,R*,^f*C*)-**38** (Scheme 8) and (*S,S*,^f*A*)-**38** were formed with a de exceeding 97% (HPLC) starting from the corresponding optically active tethered bismalonates.⁴⁷ Transesterification of (*R,R*,^f*A*)-**50** and (*S,S*,^f*C*)-**50** yielded the *cis*-3 tetraethyl esters (^f*A*)-**2** and (^f*C*)-**2** with an enantiomeric excess (ee) higher than 99% [(^f*A*)-**2**] and 97% [(^f*C*)-**2**] (HPLC), reflecting the ee

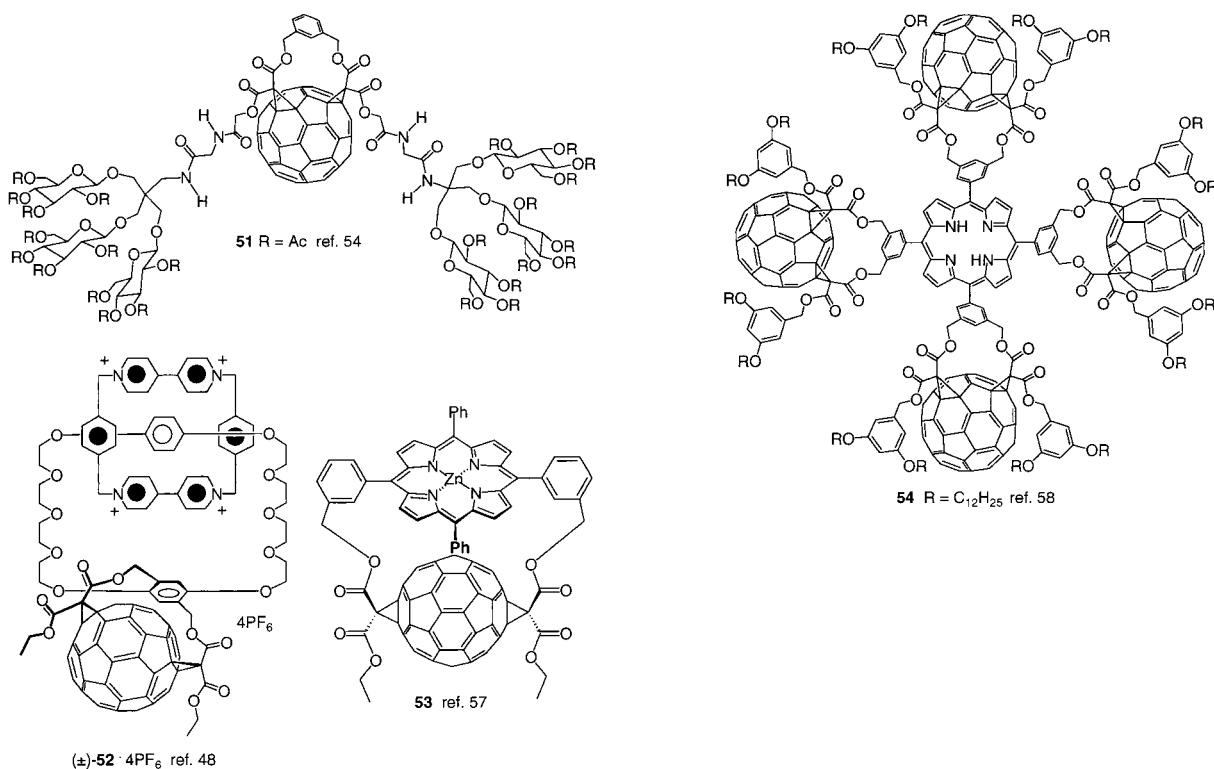
Scheme 10. Enantioselective Synthesis of (^tA)-2 and (^tC)-2 by Diastereoselective Tether-Directed Biscyclopropanation of C₆₀, Followed by Transesterification^{11c,43,45}


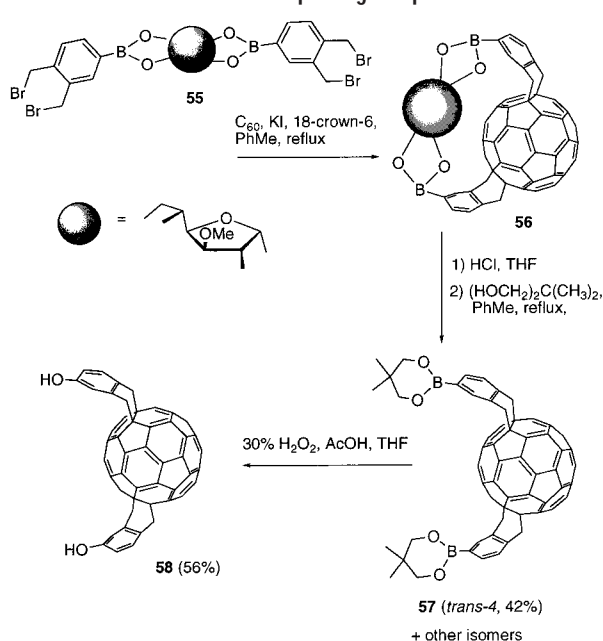
values of the corresponding commercial starting diols. The absolute configurations of these optically active fullerene derivatives were assigned from their calculated circular dichroism (CD) spectra.^{11c} An overall enantioselective synthesis of optically active C₆₀ bisadducts in which the chirality results exclusively from the addition pattern had been previously achieved by the asymmetric Sharpless osmylation; however, this (sequential) reaction lacks the regioselectivity of the Bingel macrocyclization, therefore requiring tedious regioisomer separations.⁵³ The mirror image CD spectra of enantiomeric C₆₀ derivatives with

chiral functionalization patterns such as (^tC)-2 and (^tA)-2 are characterized by large Cotton effects between 250 and 750 nm with $\Delta\epsilon$ values approaching 150 cm² mmol⁻¹.^{11b,c,45}

The Bingel macrocyclization is increasingly being exploited in the synthesis of functional supramolecular systems (Scheme 11). Thus, bisadduct **51**, a fullerene–glycodendron conjugate, was shown to form Langmuir layers at the air–water interface that are (i) monomolecular and (ii) stable and (iii) form reversibly as evidenced by the lack of hysteresis in compression and expansion cycles; in addition, monolayers of **51** could be transferred as Langmuir–Blodgett films onto quartz slides.^{54,55} By the Bingel macrocyclization, organic chromophores or receptor sites can be precisely positioned in close proximity to the fullerene surface, thus offering the potential for inducing changes in the physical properties of the carbon allotrope. This was exploited in the construction of the C₆₀-containing [2]catenane (\pm)-**52**·4PF₆⁴⁸ starting from crown ether (\pm)-**40** (Scheme 8), following the elegant self-assembly strategy developed by Stoddart and co-workers.⁵⁶ With the fullerene moiety acting as an electron acceptor, (\pm)-**52**·4PF₆ features an unprecedented intramolecular A–D–A–D–A stack (A = acceptor, D = donor).

A significant perturbation of the electronic structure of the fullerene is observed when an alkali metal cation is bound to the crown ether moiety in (\pm)-**44** (Scheme 8), which is positioned closely and tightly on the fullerene surface⁵¹ and complexes alkali metal ions, in particular K⁺, efficiently. Cyclic voltammetric studies were performed in MeCN/CH₂Cl₂ (1:1) (+ 0.1 M Bu₄NPF₆) to

Scheme 11. Examples of Functional Supramolecular Systems Constructed with the Help of the Bingel Macrocyclization (See Also (\pm)-43 and (\pm)-44 in Scheme 8)


Scheme 12. Regioselective Bisfunctionalization of C₆₀ Using a Saccharide as Imprinting Template⁶²

elucidate the effect of cation complexation on the redox properties of (\pm)-**44**. Addition of an excess of KPF_6 to a solution of (\pm)-**44** resulted in a large anodic shift (90 mV) of the fullerene-centered reduction processes, with the quasi-reversible first reduction shifting from $E_{1/2} = -1.04$ V (vs Fc/Fc⁺) in free (\pm)-**44** to $E_{1/2} = -0.95$ V in the K⁺ complex. This was the first ever observed effect of cation complexation on the redox properties of the carbon sphere in fullerene crown ether conjugates.⁵¹ A variety of macrocyclic fullerene–porphyrin conjugates have been reported, such as the cyclophane-type molecular dyads (\pm)-**43**⁴⁹ and **53**⁵⁷ with *trans*-2 and *trans*-1 addition patterns, respectively, or **54**⁵⁸ with four appended fullerenes. In these systems, the close proximity between fullerene and porphyrin chromophores leads to a nearly complete quenching of the porphyrin luminescence.

Other Tether-Directed Bisfunctionalizations of C₆₀

The principle underlying the Bingel macrocyclization is a general one, and other tethered reactive groups can be utilized for regioselective bisfunctionalizations of buckminsterfullerene.⁵² Thus, Nishimura and co-workers used bis(*o*-quinodimethanes) connected by α,ω -dioxamethylene tethers for the regioselective bisfunctionalization by double Diels–Alder addition.⁵⁹ The tethers were subsequently removed by ether cleavage. Nakamura et al. used oligomethylene-tethered bis(cyclopropanone acetals), which generate minute amounts of nucleophilic vinylcarbenes capable of undergoing 2-fold [3 + 2] cycloadditions to 6–6 bonds of the fullerene.⁶⁰ Luh and co-workers showed that bisazides connected by short tethers undergo [3 + 2] cycloadditions to neighboring 6–6 bonds, yielding, after 2-fold extrusion of N₂, bridged 1,2,3,4-bisiminofullerenes with two fused aziridine rings in a *cis*-1 addition pattern.⁶¹ An interesting templated bisfunctionalization was reported

by Shinkai and co-workers, who introduced two boronic acid groups regioselectively into the fullerene using saccharides as imprinting templates (Scheme 12).⁶² Thus, compound **55** containing 3-*O*-methyl-D-glucopyranose as template underwent a double Diels–Alder addition with C₆₀, providing as the major product the *trans*-4 bisadduct **56**.⁶² Removal of the saccharide template and boronic acid protection gave **57** (42% yield, HPLC), which was transformed into diol **58** by treatment with H₂O₂.

Conclusions

Covalent derivatives of fullerenes promise fascinating widespread applications as advanced materials in diverse technologies. Photochemical devices for conversion of solar energy into fuels and electricity, chemical and electrochemical sensors, storage and manipulation of information at the molecular level, and microfabrication of processable polymeric fullerene films with insulating or conducting properties are some of the technological applications of covalent fullerene derivatives that we foresee being successfully developed in the coming years. The templated synthesis approaches described in this account make important contributions to these exciting ventures by greatly facilitating the access to complex and highly functional fullerene building blocks for three-dimensional molecular scaffolding. We hope that the approaches presented here will further stimulate the invention of synthetic functionalization methodology to take full advantage of the outstanding technological potential of the fullerenes.

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