Reviews

Cycloaddition to buckminsterfullerene C_{60}: advancements and future prospects

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Investigations on mono-[2+1]-, -[2+2]-, -[2+3]-, -[2+4]-, and polycycloaddition to [60]fullerene are reviewed. The main reagents used in cycloaddition and the reaction mechanisms are surveyed. The possible applications of cycloadducts are considered. The review covers the investigations of the last five years as well as the most important earlier studies.

Key words: [60]fullerenes, monocycloadducts, polycycloadducts, fulleroids, cycloaddition.

Since the discovery of fullerene C_{60} and, especially, the development of procedures for its preparation in macroscopic amounts, the chemistry of fullerene derivatives has become one of the most developing fields of organic chemistry, which is of interest from both theoretical and applied points of view. Suffice it to say that the number of studies on the chemistry of fullerene published in the last five years amounts up to several thousands. The scope of a great diversity of functionalizations of the fullerene spheroid has attracted the particular attention of researchers. These functionalizations allow the design of new promising fullerene-based materials possessing unique biological and technological properties.

Being an electron-deficient polyene, fullerene C_{60} is prone to radical and nucleophilic addition reactions as well as to cycloadditions. Various [2+n]-cycloaddition reactions show considerable promise for functionalization of the fullerene sphere, the reactions with n = 1, 2, 3, and 4 being most typical.

The first two reviews concerning with some aspects of cycloadditions to [60]fullerene (see. Refs. 1 and 2) were published in 1995. The 1,3-dipolar cycloaddition reactions were surveyed in the review[3] published in 1998. The more recent review[4] on functionalizations of fullerene and prospects of the use of its derivatives surveyed only some aspects of this problem. In early extensive studies of cycloadditions to C_{60}, researchers gave priority to a search for potential addends of various cycloaddition reactions, elucidation of the major characteristic features of these processes, and preliminary examination of the useful properties of new adducts. However, trends and emphasis in investigations were somewhat changed in the last five years. By the end of 1995, the principal characteristic features of the reactivity of [60]fullerene in various cycloaddition reactions were revealed, the efficient reagents for these functionalizations were found, and the basics of mechanistical analysis were elucidated. Because of this, the majority of recent studies were focused on the target-

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directed synthesis of fullerene derivatives possessing specific useful properties, the design of fundamentally new reagents for cycloaddition, improvement in a mechanistical understanding of the cycloaddition processes, and more detailed examination of polyaddition processes and properties of polycycloadducts.

In recent years, this youngest field of organic chemistry has evolved vigorously (beginning in 1993, more than 1400 articles on the chemistry and properties of fullerenes were published annually). Hence, it is evident that the chemistry of fullerene is far from being exhausted and, hence, this field shows considerable promise from the viewpoint of theoretical, synthetic, and applied aspects. Apparently, the theoretical aspects assume a deeper insight into the mechanisms of cycloadditions, which will allow one to predict and plan the regio- and stereochemical results of mono- and polycycloadditions. From the synthetic standpoint, the future belongs evidently to the construction of new addends and the development of new cycloaddition reactions. For example, [2+*n*]-cycloadditions, where $n > 4$, remain poorly studied. This, in turn, will enable one to substantially extend the range of fullerene-based compounds with the aim of searching for new materials. Among fullerene derivatives prepared by different cycloaddition reactions, new dyes and compounds possessing unique optical, electrophysical, and biological properties have already been found. The possible useful properties have been principally studied. Therefore, the use of C_{60} derivatives in different optical and electrophysical devices in operation as well as in the design of fullerene-based pharmaceuticals are of most interest.

The present review surveys the advancements in cycloaddition reactions to [60]fullerene achieved in the last five years, the most important earlier studies also being included.

We hope that this review will be of assistance in further developing the chemistry of fullerene.

1. [2+1]-Cycloaddition

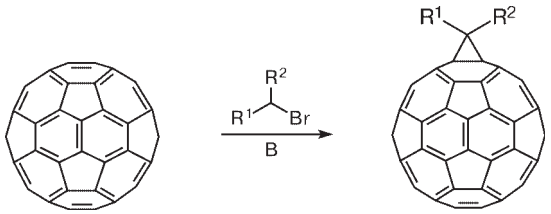
[2+1]-Cycloaddition reactions afford compounds in which the fullerene cage is fused to three-membered carbo- or heterocyclic fragments, *i.e.*, methanofullerenes, fullerenoaziridines, or fullerenooxiranes. These reactions can follow different mechanisms and involve such processes as addition of carbenes, nitrenes, and stabilized carbanions, oxidation, *etc*.

1.1. Cyclopropanation of C_{60} (methanofullerenes)

The synthetic procedures for the preparation of methanofullerenes are classified in three groups:[5] 1) reactions with stabilized carbanions proceeding by the addition—elimination mechanism; 2) addition of carbenes to C_{60}; and 3) thermal addition of diazo compounds followed by thermolysis or photolysis of the resulting intermediates.

1.1.1. Bingel reaction. Cyclopropanation of C_{60} with stabilized α-halocarbanions (the Bingel reaction)[6] is the most efficient procedure for the synthesis of methanofullerenes. It is assumed that this reaction proceeds through the initial nucleophilic addition of the stabilized α-halocarbanion to C_{60} followed by intramolecular replacement of the halogen atom by the anionic center that is generated on the fullerene sphere. The reactions proceed rapidly and, for the most part, in good yields. The classical procedure for cyclopropanation involves treatment of C_{60} with 2-bromomalonic ester in the presence of a base[6] (Scheme 1). Methanofullerenes containing different electron-withdrawing substituents in the cyclopropane moiety were synthesized analogously. Bromonitromethane in the presence of triethylamine was used as a base for the preparation of nitrocyclopropanofullerene.[7] Comparative electrochemical studies of these cycloadducts revealed a strong electron-withdrawing anomaly for the dicyano derivative (the cyano group proved to be a stronger electron acceptor as compared to that predicted based on the Hammett correlation). This fact was attributed to conjugation through the cyclopropane ring as well as to irreversible processes attendant on the attachment of the electron to the fullerene sphere.

Scheme 1



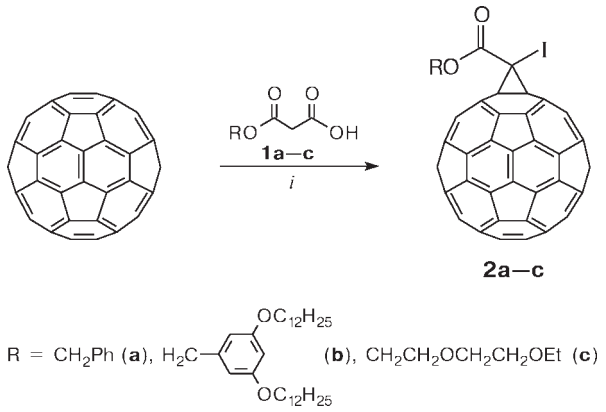
$R^1 = R^2 = CO_2Me$ (27%), CN (66%);
$R^1 = CO_2Et$, $R^2 = CN$ (47%); $R^1 = H$, $R^2 = NO_2$ (32%)*

B is a base.

The modified procedure involves the *in situ* formation of 2-bromo- or 2-iodomalonates. In this case, C_{60} is treated with malonic ester in the presence of I_2 [8,9] or CBr_4 [10] and a base. This reaction follows an unusual pathway upon treatment of C_{60} with malonic acid monoesters **1a—c** in the presence of iodine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base. The reaction unexpectedly afforded[5] 61-iodo-1,2-methano[60]fullerene-61-carboxylates **2a—c** in yields from 25 to 28% (Scheme 2).

* Hereinafter, the yields are given with respect to consumed fullerene.

Scheme 2

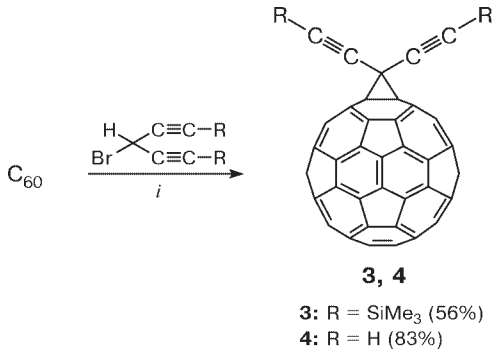


i. I_2, DBU, toluene, ~20 °C, 24 h.

The formation of compounds **2a—c** is conceivably associated with the fact that fullerene derivatives of malonic acid are readily decarboxylated under basic conditions to form the carbanion, which reacts with I_2.

An analogous Bingel-type transformation can be performed with the use of 3-bromo-1,5-bis(trimethylsilyl)penta-1,4-diyne instead of 2-halomalonic esters. In the presence of DBU, this diyne produced bis(trimethylsilylethynyl)methanofullerene **3**. Desilylation of the latter with potassium carbonate in methanol gave rise to compound **4**, which can be considered as a new allotropic form of carbon[11] (Scheme 3).

Scheme 3

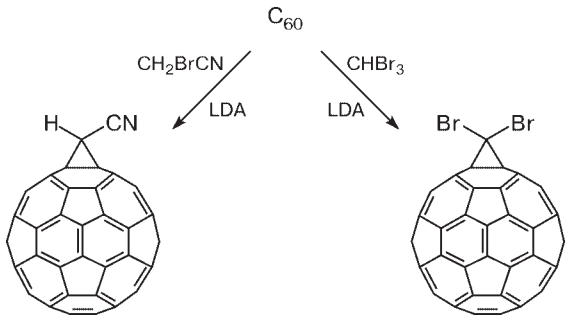


i. DBU (2 equiv.), toluene, ~20 °C, 2 h.

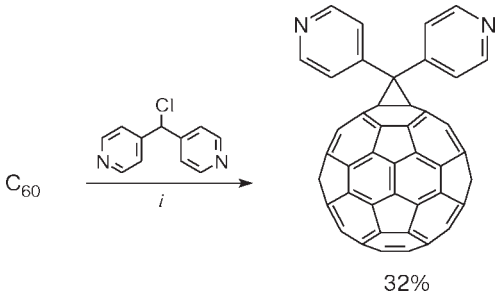
Cyclopropanation can also take place upon treatment of C_{60} with bromoacetonitrile or bromoform in the presence of lithium diisopropylamide (LDA) to form cyano- and dibromocyclopropanofullerenes,[12] respectively (Scheme 4).

Bis(4-pyridyl)chloromethane was also used as the starting compound for generation of the stabilized carbanion under the conditions of the Bingel reaction (Scheme 5).[13]

Scheme 4



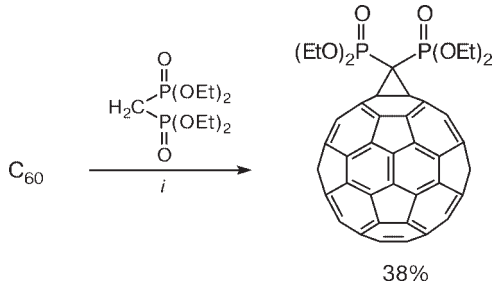
Scheme 5



i. DBU, toluene, ~20 °C.

The versatility of this procedure can be exemplified by the preparation of new phosphonate derivatives of [60]fullerene[14,15] (Scheme 6).

Scheme 6

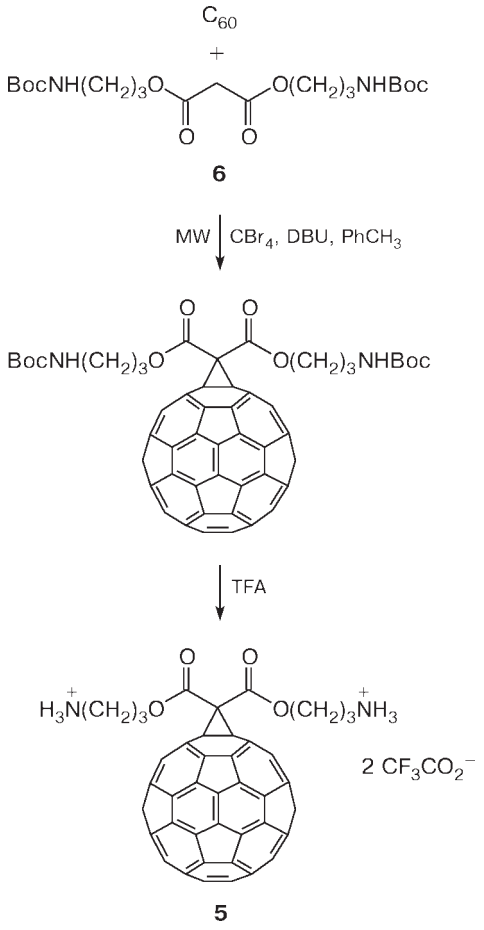


i. I_2, DBU, toluene, ~20 °C.

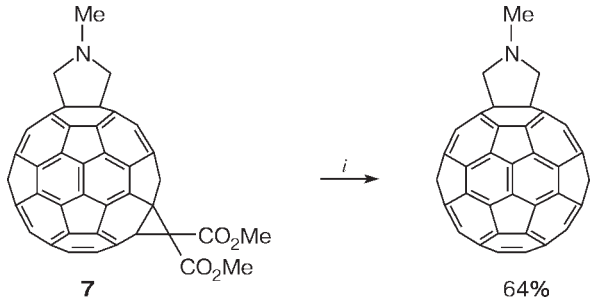
Acceleration of cycloaddition under microwave (MW) irradiation was used for the preparation of water-soluble methanofullerene-based bis-ammonium salt **5**. The reaction was carried out with the use of 1.5 equiv. of protected aminomalonate **6**, 1 equiv. of C_{60}, 1.5 equiv. of CBr_4, and 3 equiv. of DBU followed by removal of the protective carbamate group with trifluoroacetic acid[16] (Scheme 7).

Since a great diversity of malonate derivatives are readily available, the Bingel reaction is widely used for

Scheme 7



Scheme 8

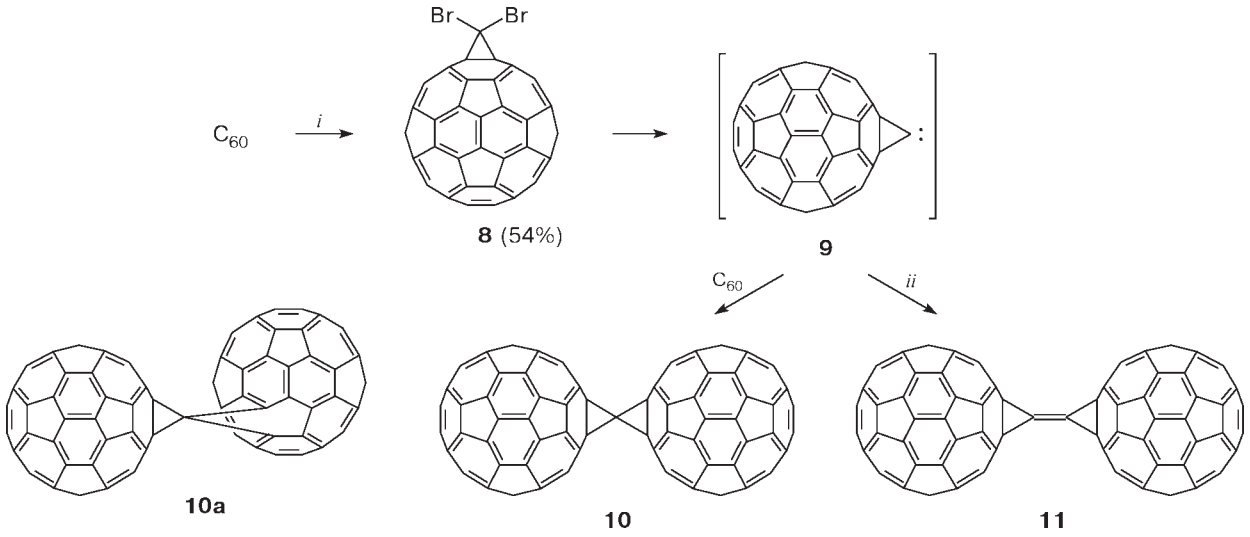


i. Mg/Hg, THF, Ar, 80 °C, 3 days.

functionalization of the fullerene sphere in target-directed syntheses of new compounds possessing useful properties. For example, this process was used for the preparation of water-soluble dendro[60]fullerenes,[17,18] new organic ligands based on C_{60},[19] and photosusceptible multicomponent donor-acceptor systems involving phthalocyanine or porphyrin systems as donor components, the chromophoric groups being linked by different crown ethers.[20—24]

Another characteristic feature of classical Bingel adducts, *viz.*, bis(alkoxycarbonyl)methanofullerenes, is great synthetic importance. Recently, it was found that under the action of magnesium amalgam in dry THF, these adducts were readily subjected to the selective retro-Bingel reaction. For example, only the bis(alkoxycarbonyl)methane addend was removed[25] in the case of bis-adduct **7** (Scheme 8). The mechanism of the electrochemical retro-Bingel reaction was also investigated.[26]

Scheme 9



Reagents and conditions: *i.* $PhHgCBr_3$, benzene, reflux; *ii.* dimerization.

Hence, bis(alkoxycarbonyl)methane addends can be used as protective orienting groups for regioselective polyfunctionalization of fullerenes.

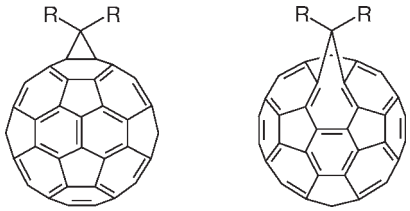
1.1.2. Reactions with carbenes. An alternative approach to cyclopropanation of [60]fullerene is based on the use of carbenes in [2+1]-cycloaddition reactions.

As expected, the addition of singlet carbenes to electron-deficient polyene C_{60} proceeds in one step exclusively at the double 6,6-bond of fullerene.[27] Actually, the reaction of fullerene with dibromocarbene generated from the Soifert reagent ($PhHgCBr_3$) afforded 61´,61´-dibromo-1,2-methano[60]fullerene[28] (Scheme 9).

Moreover, mass-spectrometric analysis[28] of the reaction mixture revealed the presence of dumbbell-like C_{121} (**10**) and C_{122} (**11**) molecules, which are new allotropic forms of carbon. The latter are generated apparently through carbene intermediate **9** by the reaction with C_{60} or dimerization, respectively. Later on, a mixture of compounds **10** and **11** was prepared upon thermal generation of carbene **9** from dibromide **8** at 450 °C [29] or by the reaction of C_{60} with diazotetrazole as the carbene source.[30] However, the recent detailed study of the thermal reaction of dibromide **8** with C_{60} revealed the formation not only of symmetrical fullerene dimer **10** but also of isomeric unsymmetrical dimer **10a** containing both the fullerene and fulleroid (see also Section 1.1.3) moieties.[31]

New methanofullerene-containing stable phosphorus ylide was prepared by the reaction of C_{60} with a mixture of triphenylphosphine and dimethyl acetylenedicarboxylate (1 : 1)[32] through [2+1]-cycloaddition of the carbene or anionic intermediate (Scheme 10).

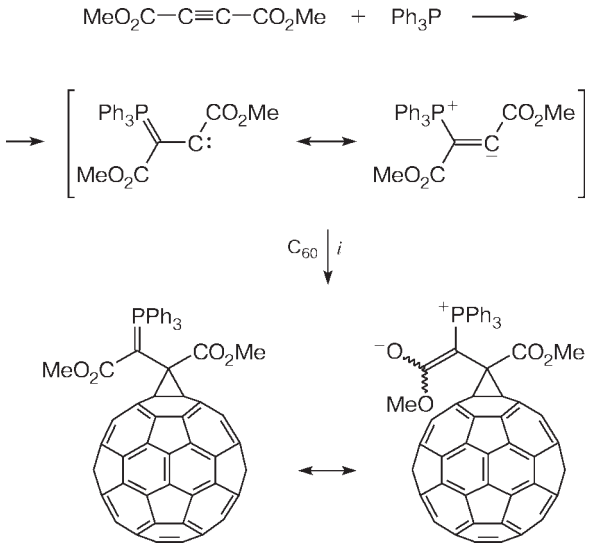
1.1.3. Reactions with diazo compounds. Diazo compounds have found wide use as precursors of carbenes. However, the thermal addition of diazo compounds to fullerene is a more complex process than that with the involvement of singlet carbenes generated according to other methods (see, for example, Ref. 27). This is associated with the formation (depending on the structure of the diazo compound and the reaction conditions) of a mixture of [6,6]-closed (fullerene) and [6,5]-open (fulleroid) isomeric cycloadducts.



[6,6]-closed [6,5]-open

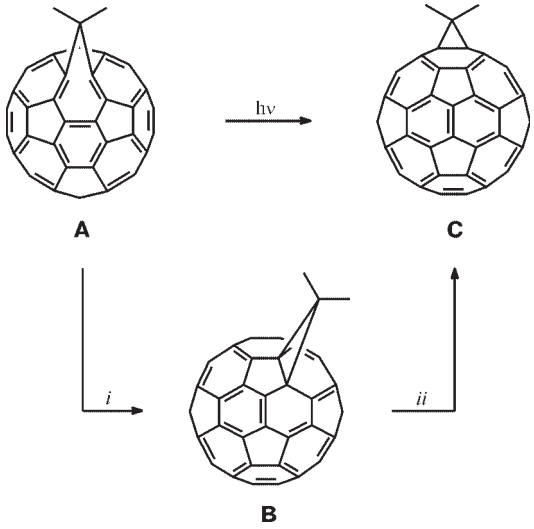
In the general case, there are several possible reasons for this phenomenon. First, two mechanisms of cyclopropanation in the case of the thermal reaction of C_{60} with diazo compounds are conceivable: a) initial thermal decomposition of diazo compounds to form carbenes followed by their concerted addition to the double 6,6-bond of fullerene or b) initial 1,3-dipolar cycloaddition of diazo compounds to fullerene followed by nitrogen elimination from the pyrazoline intermediate. The last-mentioned pathway can afford both isomers.[33] Second, the rearrangement of [6,5]-open isomers into thermodynamically more

Scheme 10



i. Toluene, 110 °C, 12 h.

Scheme 11



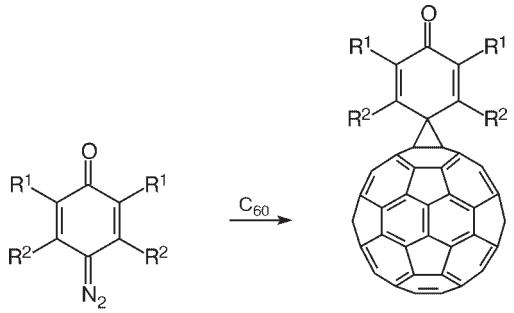
A — [6,5]-open, **B** — [6,5]-closed, **C** — [6,6]-closed fullerene.

i. Disrotatory. *ii*. [1,5]-sigmatropic shift.

stable [6,6]-closed isomers can take place. Thus, it has been demonstrated convincingly[34] that a series of [6,5]-open fulleroids containing stabilizing substituents in the methane bridge were rearranged into [6,6]-closed fullerenes both according to the zero-order kinetic photochemical process and by the high-energy monomolecular mechanism involving disrotatory closure to form [6,5]-closed fullerene, which was subsequently rearranged into [6,6]-closed fullerene through a biradical intermediate (Scheme 11).

It should be noted that examples of the addition of diazo compounds to C_{60} producing either mixtures of isomeric fullerene and fulleroid derivatives or selectively yielding the individual isomeric cycloadduct as the only product were reported in recent years. Thus, the reactions of fullerene with quinoid-type diazo compounds **12a—d** in *o*-dichlorobenzene performed on heating or photochemically under an atmosphere of nitrogen afforded exclusively [6,6]-closed spiromethanofullerenes **13a—d** (Scheme 12).[35]

Scheme 12



12a—d **13a—d**

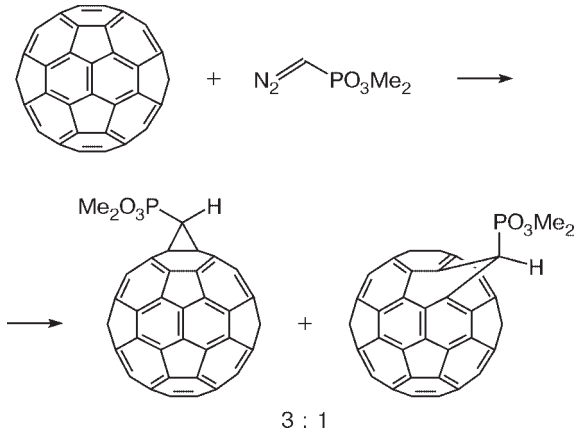
Compound	R^1	R^2	Conditions			Yield (%)
			Irradiation	*T*/°C	τ/h	
13a	H	H	*hν*	0—10	1	47
13b	Me	H	*hν*	0—10	1	43
13c	Bu^t	H	*hν*	0—10	2	57
13d	$(—CH=CH—)_2$		—	60—70	24	65

Note. τ is the reaction time.

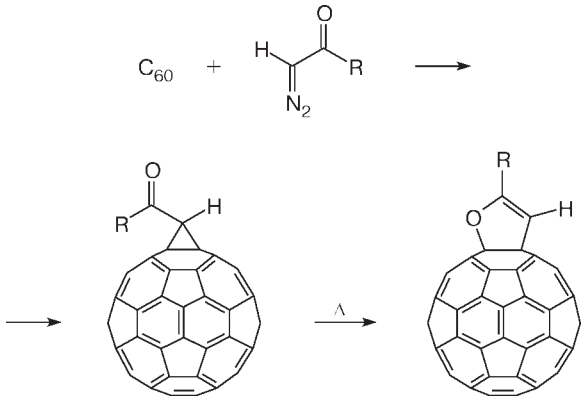
Apparently, thermal addition (110 °C, toluene) of dimethyl diazomethylphosphonate to C_{60} gave rise to a mixture of isomeric fullerene and fulleroid cycloadducts in a ratio of 3 : 1 (Scheme 13).[15]

In the course of thermal (100—150 °C) addition of α-diazoketones to fullerene, the initially formed (in 25—35% yields) [6,6]-closed methanofullerenes were rearranged into [6,6]-bridged closed 2′-substituted 1,2-dihydro(4′,5′-dihydrofurano)[60]fullerenes (the yields were 18—21%) (Scheme 14).[36]

Scheme 13



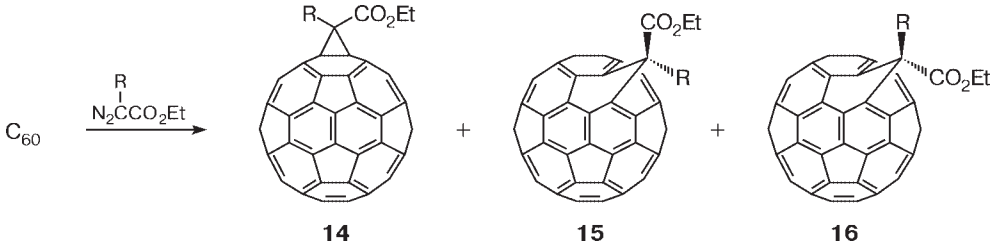
Scheme 14



The first example of transition metal catalysis of the carbenoid reaction of C_{60} was reported.[37] The use of $Rh_2(OAc)_4$ as a catalyst for generation of alkoxycarbonyl carbenoids from ethyl diazoacetate and ethyl diazomalonate in the reaction with C_{60} allows one to increase the yields and improve the selectivity of the process as compared to the conventional thermal reactions (Scheme 15).

One of approaches to the *in situ* generation of unstable diazo compounds is based on the use of stable hydrazones and their derivatives. This is particularly true in regard to oxidation of hydrazones with MnO_2.[38,39] It was assumed[40] that cyclopropanation proceeds through the initial 1,3-dipolar cycloaddition of a diazo compound to C_{60} followed by nitrogen elimination from the resulting pyrazoline intermediate. The reaction gives rise to a mixture of [6,6]-closed and [6,5]-open derivatives. This procedure was used for the insertion of the methane bridge containing fragments of benzocrown ethers[38] or the "pincer" ligand[39] with the aim of examining the complex-forming properties of new fullerene derivatives (Scheme 16).

Scheme 15

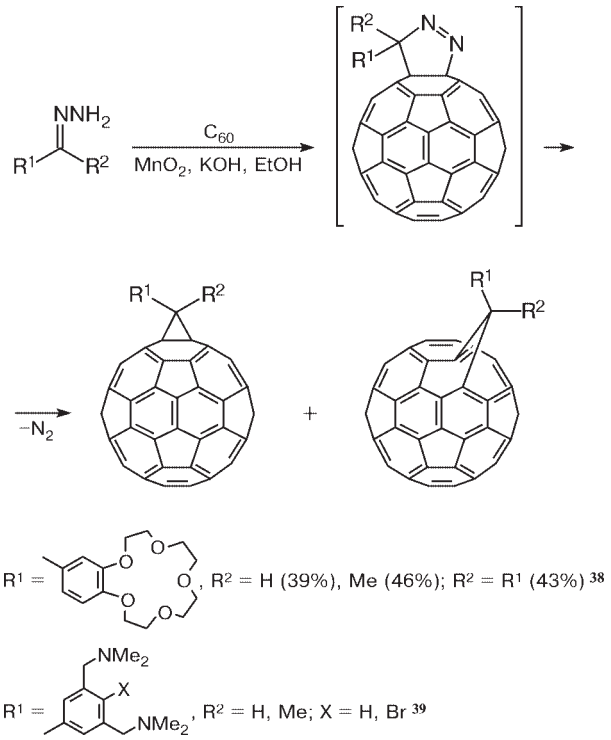


14 is a [6,6]-closed isomer, **15** and **16** are [6,5]-open isomers.

R	Conditions				Yield (%)	Ratio **14** : **15** : **16**
	Treatment	Solvent	*T*/°C	τ/h		
H	Heating	Toluene	110	7	35	1 : 4 : 2
H	$Rh_2(OAc)_4$	Toluene	20	20	21	14 : 1 : 1
H	$Rh_2(OAc)_4$	1-Methylnaphthalene	20	8	42	52 : 1 : 0
CO_2Et	Heating	Toluene	110	20	10	Not determined
CO_2Et	$Rh_2(OAc)_4$	1-Methylnaphthalene	80	32	9	1 : 0 : 0

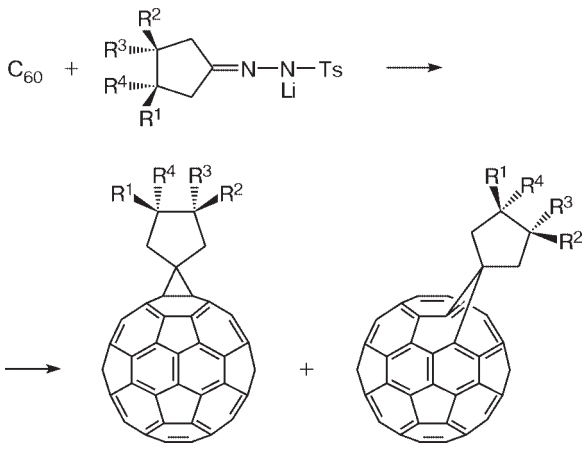
Note. τ is the reaction time.

Scheme 16



Diazo compounds can be generated not only by oxidation of unsubstituted hydrazones but also by thermolysis of lithium or sodium salts of tosylhydrazones.[40—44] In the latter case, mixtures of [6,6]-closed and [6,5]-open isomeric cycloadducts were also obtained. However, in the case of thermolysis of fullerene and lithium salts of cycloalkylidenetosylhydrazones in refluxing toluene, the conditions were optimized for the predominant formation of fulleroid derivatives. This was achieved by decreasing the reaction time. As a result, the yield of the kinetically controlled product was increased. When the processes was carried out over a longer period, methanofulleroid was rearranged into thermodynamically more stable [6,6]-closed methanofullerene.[40]

Scheme 17

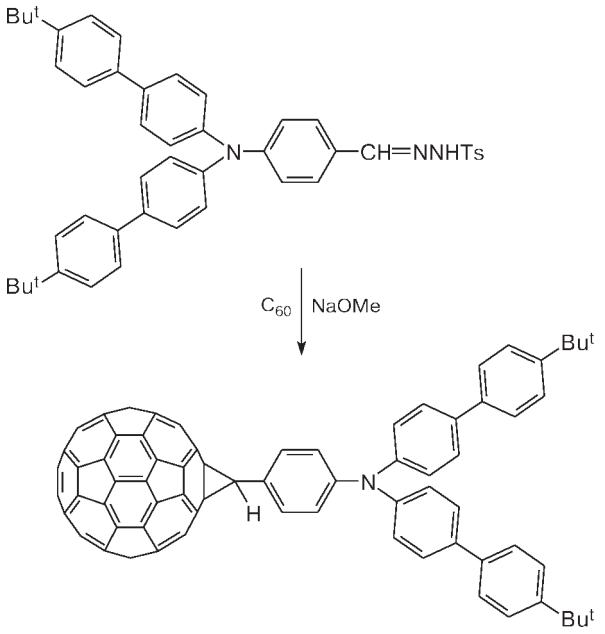


R^1 = H, CO_2Et, CO_2Me; R^2 = H, CO_2Et; R^3 = H, CO_2Et, CO_2Me; R^4 = H

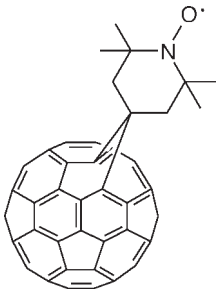
The highest yield (67%) and the best ratio between the [6,5]-open and [6,6]-closed isomers (13.3 : 1) were achieved for the compound with $R^1 = R^3 = CO_2Me$ and $R^2 = R^4 = H$ when the reaction was carried out for 25 min, whereas these values were 23% and 1.7 : 1, respectively, in the case of the longer reaction time (90 min).

To the contrary, the reaction of C_{60} with hydrazone containing the electron-donating *p*-diarylaminoaryl substituent in the presence of sodium methoxide in *o*-dichlorobenzene afforded only the thermodynamically more stable [6,6]-closed isomer even at rather low temperature (40 °C)[45] (Scheme 18).

Scheme 18



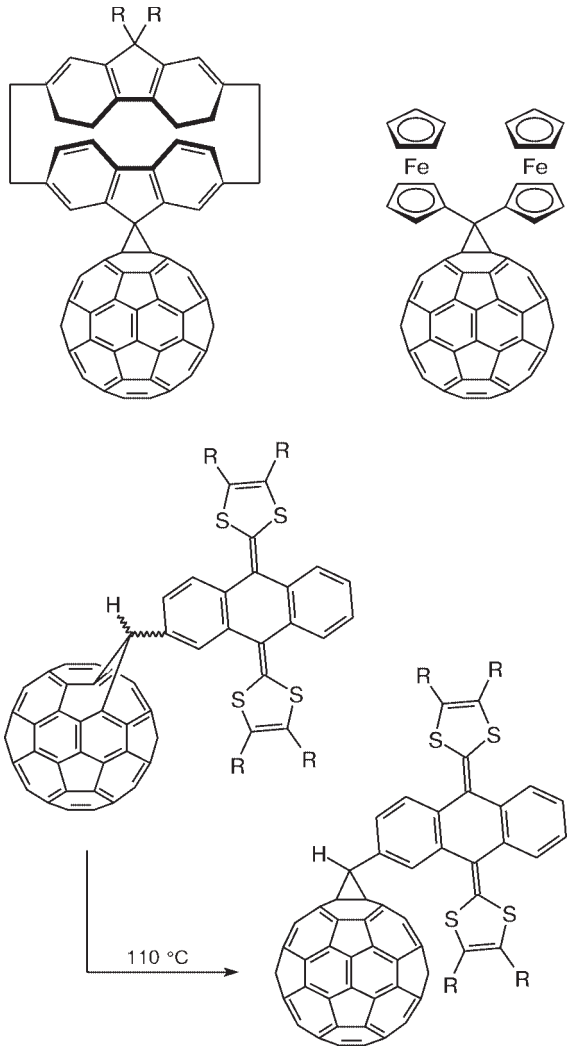
An analogous procedure was used for the functionalization of [60]fullerene with the 2,2,6,6-tetramethylpiperidine-1-oxyl radical;[41] however, in this case only the open fulleroid isomer was obtained in ~25% yield.



The broad synthetic scope of the procedure can be exemplified by the insertion of such residues as [2.2](2,7)fluorenophane,[42] bis-ferrocenyl,[43] or tetrathiafulvalene[44] groups at the bridgehead position of the methane fragment. In the latter case, the reaction performed under kinetically controlled conditions at 70 °C afforded [6,5]-fulleroids, which were thermally (110 °C) rearranged into thermodynamically more stable [6,6]-closed isomers (Scheme 19).

Instability of aliphatic diazo compounds substantially hinders the control over the addition to C_{60}, which proceeds in low yields. In the study,[46] these difficulties were overcome by *in situ* generation of the diazo compound from the stable precursor, *viz.*, the corresponding urea derivative **17** (Scheme 20).

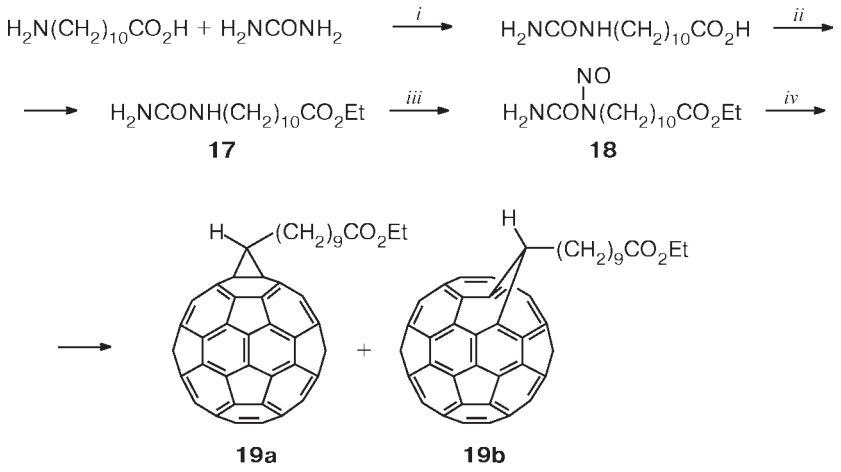
Scheme 19



Nitrosation of compound **17** gave rise to nitroso derivative **18**, which was subsequently used without purification. The amount of the diazo compound generated from **18** was controlled by the rate of addition of KOH. In this case, unlike the previous studies, [6,5]-open isomer **19b** appeared to be thermodynamically more stable. This isomer was obtained upon the rearrangement of the initially formed [6,6]-closed cycloadduct **19a** (according to the NMR spectroscopic data). This transformation was accounted for by the effect of the bulky aliphatic substituent at the bridgehead position. Since the addition of KOH to nitroso compound **18** led to immediate nitrogen elimination and the pyrazoline intermediate was never detected in the reaction products, it was concluded that the carbene mechanism is realized in this reaction.

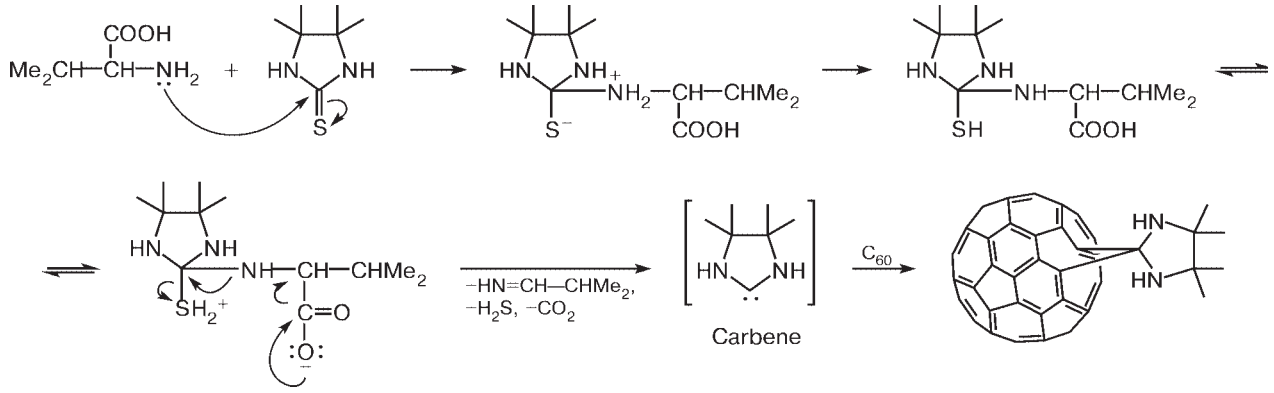
The unexpected mode of carbene generation was observed in the reaction of C_{60} with DL-valine and

Scheme 20



Reagents and conditions: *i*. Py, Δ; *ii*. H_2SO_4, EtOH, PhH, Δ; *iii*. $NaNO_2$—AcOH, 0—5 °C; *iv*. C_{60}, KOH, toluene, 20 °C, 24 h.

Scheme 21



4,4,5,5-tetramethylimidazoline-2-thione.[47] The reaction proceeded according to Scheme 21 to give the corresponding spirofused fulleroid.

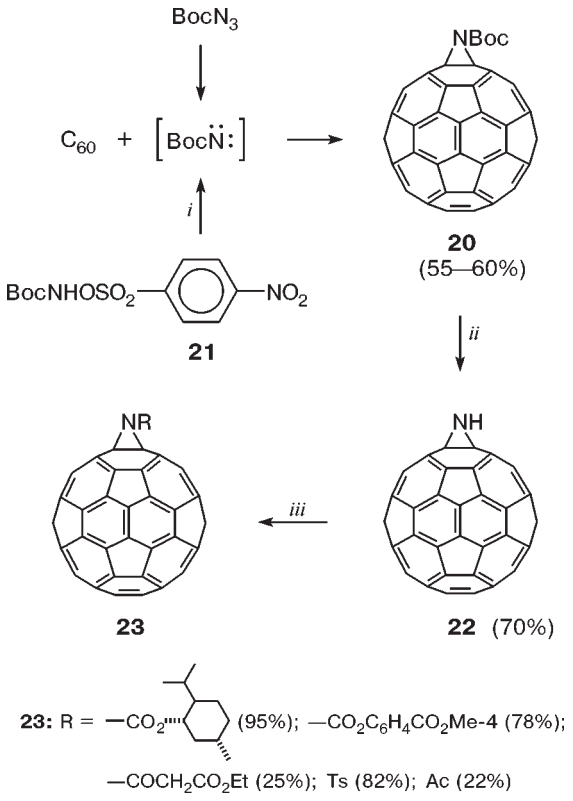
1.2. Fullerenoaziridines

Nitrenes, which are nitrogen analogs of carbenes, behave analogously in cycloaddition to [60]fullerene. These compounds are most commonly generated *in situ* by thermal decomposition of azides. For example, the addition of *tert*-butyl azidoformate to C_{60} in 1,1,2,2-tetrachloroethane at 147 °C proceeded with nitrogen elimination to form very rapidly (the reaction was completed in a matter of minutes) *N*-*tert*-butyloxycarbonyl[60]fullereno[1,2-*b*]aziridine (**20**). An analogous result was achieved under milder conditions of the nitrene generation, *viz*., upon base-initiated α-elimination of 4-nitrophenylsulfonic acid from compound **21** in the presence of C_{60} under the phase-transfer conditions at room temperature[48] (Scheme 22). Subsequent thermal elimination of CO_2 from compound **20** or elimination of the *tert*-butoxycarbonyl group upon chromatography on neutral aluminum oxide with chloroform as the eluent[49] allowed unsubstituted fullerenoaziridine to be readily isolated as a stable solid compound. Acylation of this unsubstituted fullerenoaziridine afforded water-soluble derivatives **23** (urethanes, amides, or sulfonamides).[50]

Besides, *N*-(4-R-benzoyl)fullerenoaziridines **24** with R = OMe, CN, H, or Br are also of great synthetic importance. These compounds can be rearranged into [6,6]-closed fullerenooxazoles in very high yields (90—97%) upon refluxing in tetrachloroethane or under irradiation[51] (Scheme 23).

A more careful investigation on the addition of azidoformate $BocN_3$ to C_{60} revealed the minor isomer (10%) whose structure was erroneously assigned to the previously unknown [6,5]-closed isomer.[52] Later on, this conclusion was vigorously rejected based on the detailed analysis of the spectroscopic data. The structure of the [6,5]-open isomer of fulleroid was reassigned to the minor isomer.[53,54]

Scheme 22

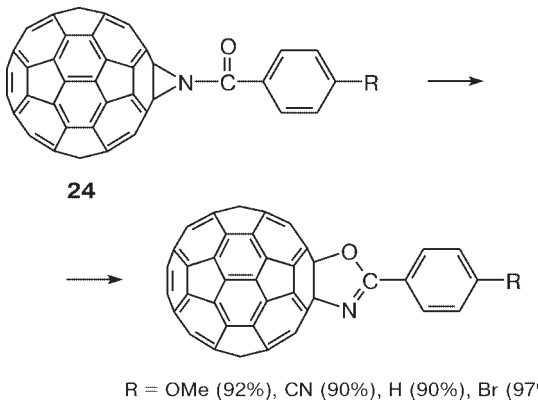


Reagents and conditions: *i*. $NaHCO_3$, H_2O—$C_2H_2Cl_4$—$BnNEt_3Cl$; *ii*. 147 °C, 5 h; *iii*. RCl, 1,2-$Cl_2C_6H_4$, Py, 70 °C.

However, [6,5]-closed isomer **26a** was found for the first time along with [6,5]-open isomer **26b** and [6,6]-closed isomer **27** in the recent study of cycloaddition of isocyanuratoalkyl azide **25** to [60]fullerene (Scheme 24). Its structure was unambiguously established by spectroscopic methods.[55,56]

The authors of the cited study demonstrated that [6,5]-closed isomer **26a** can be isolated in preparative amounts by performing the reaction of C_{60} with 1,3-diallyl-5-(5-azidopentyl)-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione at 100 °C. In the course of thermolysis, this isomer was successively transformed into [6,5]-open isomer **26b** and finally into thermodynamically more stable [6,6]-closed fullerenoaziridine **27**. Under more drastic conditions (180 °C), the reaction of 1,3-bis(cyanoethyl) azide afforded closed adduct **27** along with nitrene dimerization product **28**. This result provides support for the fact that the nitrene mechanism is realized at high temperatures.

Scheme 23



Electrochemical studies of [6,5]-open isomer **26b** by cyclic voltammetry revealed three reversible reduction peaks at less negative potentials than those observed for C_{60},[57] which is apparently attributed to the intramolecular effect of the isocyanurate substituent on the fullerene moiety. Alternatively, this fact can be accounted for by the intramolecular through-space interaction between the fullerene sphere and the isocyanurate moiety.

The availability of a wide range of aliphatic and aromatic azides offers considerable synthetic possibilities for functionalization of the fullerene sphere using cycloaddition. For example, this method was used for the functionalization of fullerene by the pharmacophore acridine function, which is known to be active with respect to DNA[58] (Scheme 25).

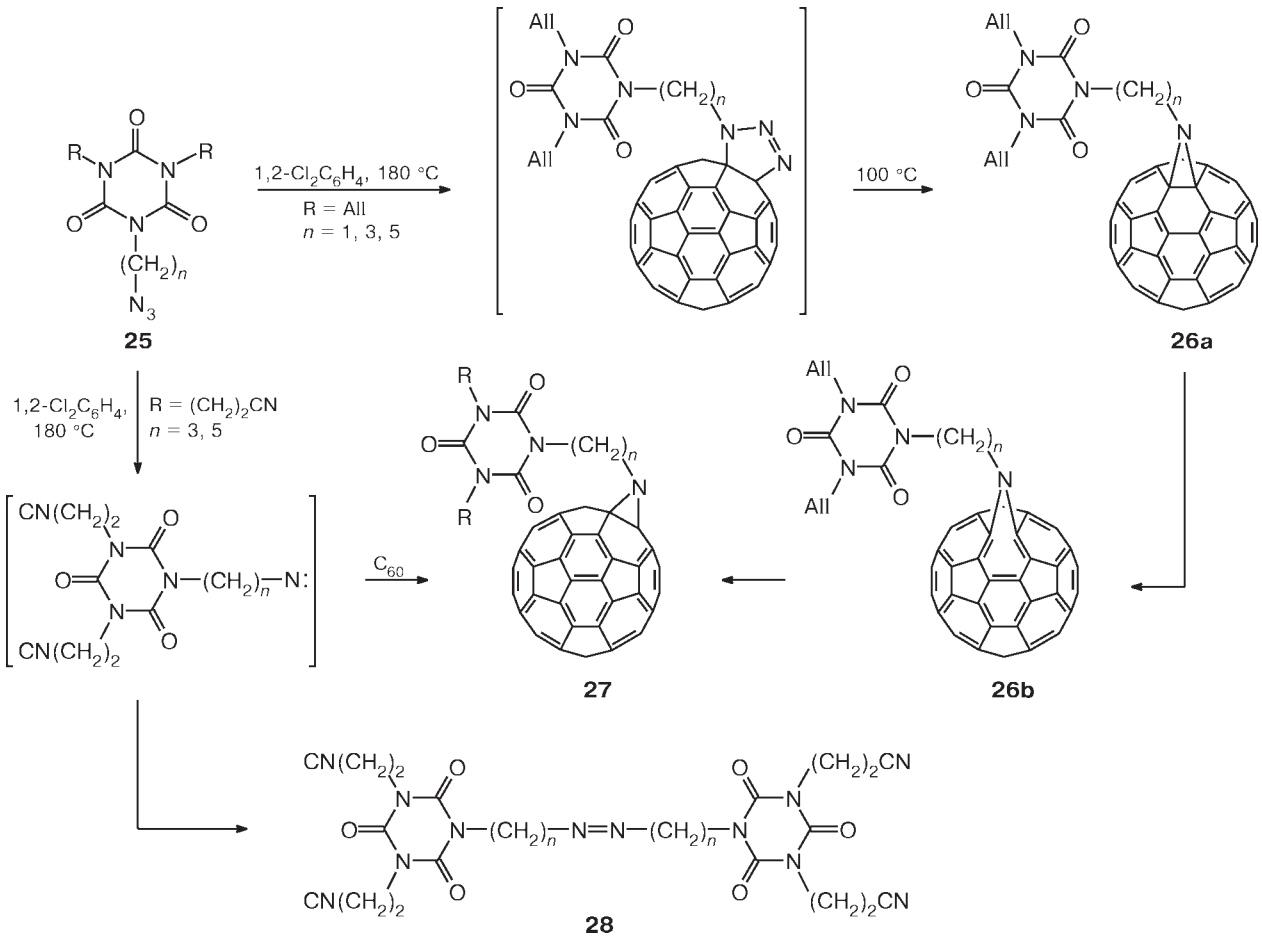
Cycloaddition of tetra-*O*-acetylglycosyl azides to C_{60} was used for the preparation of fullerene glycoconjugates[59] (Scheme 26).

This approach was also applied to the synthesis of new fullerene-porphyrin hybrids wherein both functions are linked by a polyester spacer.[60] In the last three cases, fulleroid cycloadducts are formed.

It was attempted to solve the question about the direction of cycloaddition depending on the structure of azide using aryl and hetaryl azides as an example.[61] It is known that the concerted addition of nitrene occurs at the double 6,6-bond to form closed aziridinofullerenes, whereas the initial 1,3-dipolar cycloaddition yielding the triazoline intermediate followed by nitrogen elimination leads to [6,5]-open π-azafulleroids. Actually, the reactions of aryl azide **29** and hetaryl azide **30** proceeded differently to give [6,6]-closed and [6,5]-open cycloadducts, respectively (Scheme 27). However, no explanation was provided for the observed differences.

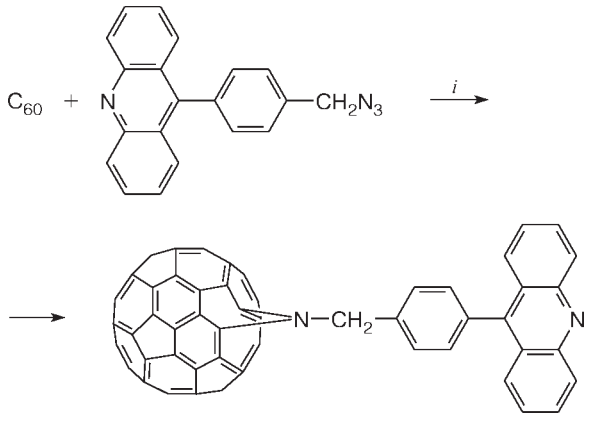
The mechanism of 1,3-dipolar cycloaddition of methyl azide to [60]fullerene followed by nitrogen elimination was theoretically substantiated based on the results of semiempirical and density functional quantum-chemical calculations.[62] It was found that the addition proceeds at the double 6,6-bond to give a closed triazoline intermediate. At the B3LYP/6-31G*//AM1 level of theory, the energy barrier to this cycloaddition is ~20 kcal mol^{-1} and the exothermicity is ~2 kcal mol^{-1}. Subsequent thermal elimination of nitrogen proceeds by the stepwise mecha-

Scheme 24



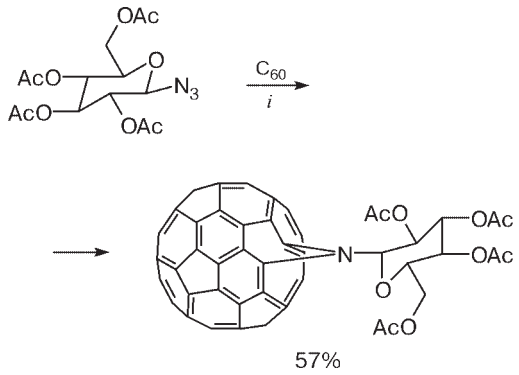
nism in which the cleavage of the N—N bond precedes the cleavage of the C—N bond. The total activation energy was determined to be about 45 kcal mol^{-1}. The N_2 expulsion from the intermediate products was accompanied by the formation of the new C—N bond. In this reaction step, the steric effect of the leaving N_2 molecule prevents the attack of the nitrene nitrogen atom on the

Scheme 25



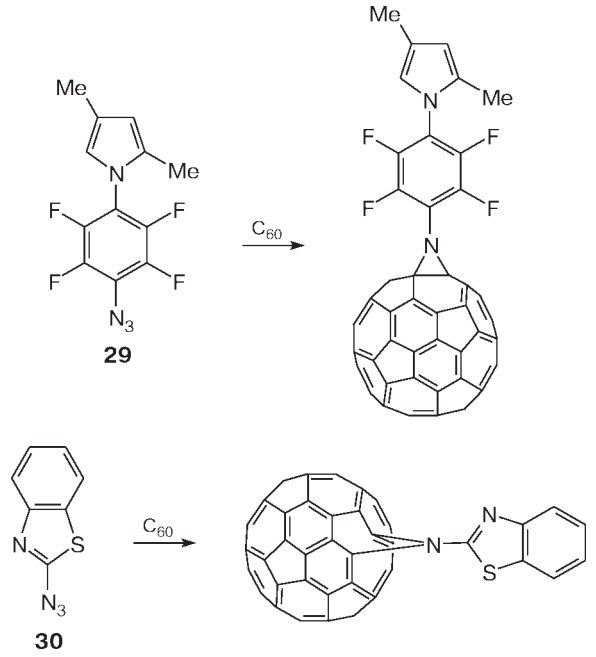
i. 1,2-$Cl_2C_6H_4$, 130 °C, 2 h.

Scheme 26



i. PhCl, Δ, 7—10 h.

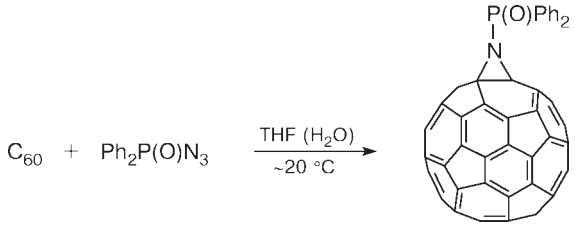
Scheme 27



6,6-bond and increases the contribution of the attack on the 6,5-bond.

Besides the numerous conventional addition reactions of azides, one example of the use of phosphoryl azide is available in the literature. Thus, the monoadduct of [2+1]-cycloaddition to the double 6,6-bond, *viz.*, *N*-(diphenylphosphoryl)[60]fullereno[1,2-*b*]aziridine, was detected by mass spectrometry among other products of the reaction of diphenylphosphoryl azide with [60]fullerene.[63] This example shows once again that azides with diversified substituents can be used in cycloaddition reactions (Scheme 28).

Scheme 28

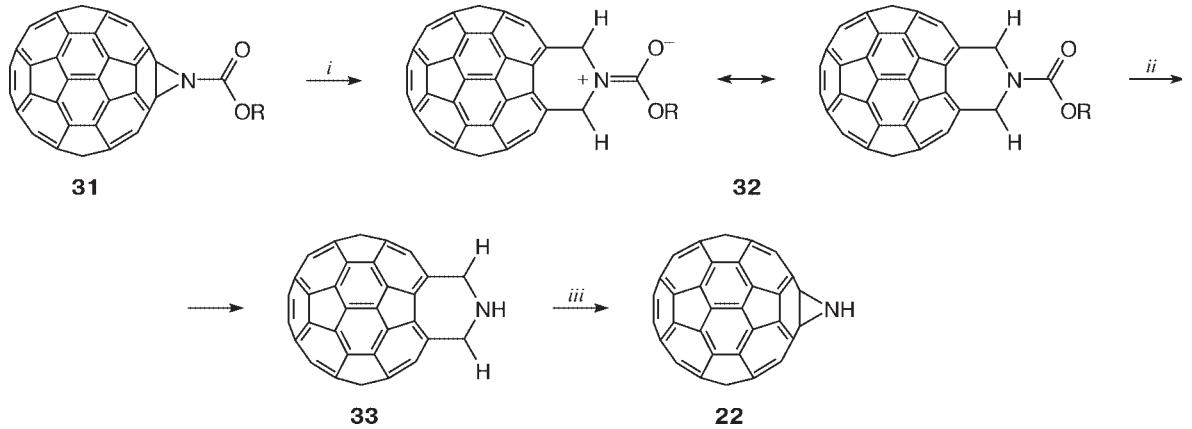


The unexpected expansion of the fullerene cage was observed upon reduction of *N*-alkoxycarbonyl[60]fullereno[1,2-*b*]aziridine (**31**) with Zn or Mg in glacial acetic acid.[64] In the course of this reduction, the reversible cleavage of the C—C bond was observed to produce compounds **32**, which is the first representatives of fullerenes compound with a bridge at the open 6,6-bond. The removal of the *tert*-butoxycarbonyl protective group (R = Bu^t) by treating with a 50% aqueous solution of TFA provides a convenient approach to the synthesis of $C_{60}H_2NH$ (**33**), which is a parent compound of a new class of fullerenes. Under the action of bases, such as 1,4-diazabicyclo[2.2.2]octane, compound **33** was transformed into fullerenoaziridine **22** in a few minutes (Scheme 29). This reaction has the general character. Under reducing conditions, compounds **31** bearing various substituents R (R = Bu^t, Et, Cl_3CCH_2, or 9-fluorenylmethyl) were transformed into compounds **32** in yields of >90%.

1.3. Epoxidation of fullerenes

Oxidative [2+1]-cycloaddition to [60]fullerene giving rise to fullerenooxiranes have received much less attention in recent years. These studies concerned primarily the search for new oxidazing agents and optimization of the conditions for the preparation of monoadducts. Thus, it was demonstrated that oxidation of C_{60} with hydrogen

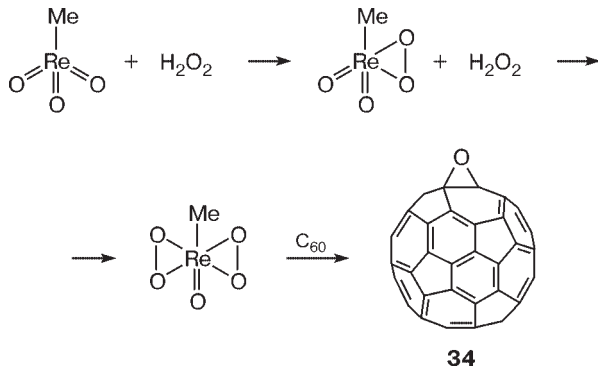
Scheme 29



Reagents and conditions: *i*. Zn, AcOH; *ii*. TFA (aq.); *iii*. 1,4-diazabicyclo[2.2.2]octane.

peroxide catalyzed by methyltrioxorhenium afforded $C_{60}O$ (**34**) in higher yields as compared to other methods of oxidation. The highest yield of the monoxide was 35%.[65] Further oxidation yields polyoxides (Scheme 30).

Scheme 30



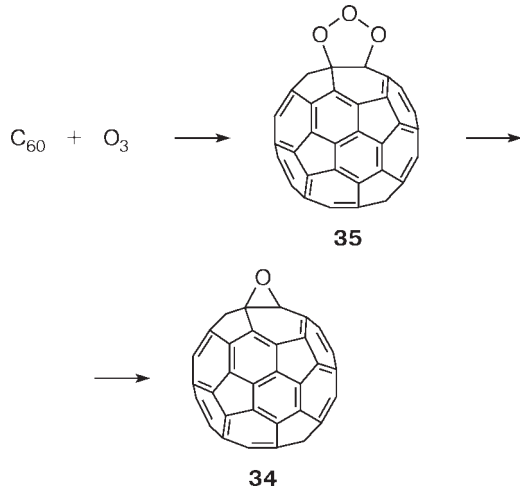
34

Epoxidation of [60]fullerene with various oxidizing agents, such as dimethyldioxirane, methyl(trifluoromethyl)dioxirane, and bis(trifluoromethyl)dioxirane, was theoretically studied by quantum-chemical AM1 calculations.[66] These calculations demonstrated that the process involving dimethyldioxirane has inverse electron demand with the interaction between HOMO of oxirane and LUMO(π^*) of fullerene and proceeds through the "spiro" transition state. The introduction of the CF_3 groups into dioxirane molecules leads to a decrease in energy of LUMO of peroxide and these oxiranes are involved in normal electron demand cycloaddition to fullerene. Hence, oxidation with trifluoromethyloxiranes proceeds faster and more efficiently to give a monooxidation adduct in higher yield.

An unstable intermediate was detected and isolated upon ozonation of C_{60} in solution.[67] The ozonide structure was assigned to this compound based on the data from UV spectroscopy, the results of measurements of the amount of oxygen liberated upon transformation of this intermediate into epoxide, and the first-order kinetics of decomposition. This [6,6]-closed adduct **35** of ozone with fullerene dissociates to form fullerenooxirane **34** and oxygen in a toluene solution, in octane, and in the solid phase with the rate constants (at 23 °C) of $4.6 \cdot 10^{-2}$, $1.3 \cdot 10^{-3}$, and $3.0 \cdot 10^{-3}$ min^{-1}, respectively (Scheme 31).

Most of the studies on the preparation of fullerene oxides were carried out before 1995. Although these studies are being continued, they attract much less attention as compared to other cycloaddition reactions. Apparently, this is associated with the fact that these cycloadducts are of limited application. In our opinion, these compounds can be used in the nucleophilic cleavage of the epoxide ring for the construction of new compounds of the

Scheme 31



35

34

fullerene—spacer—donor type. However, the results of such investigations, as far as we know, are lacking in the literature.

2. [2+3]-Cycloaddition to [60]fullerene

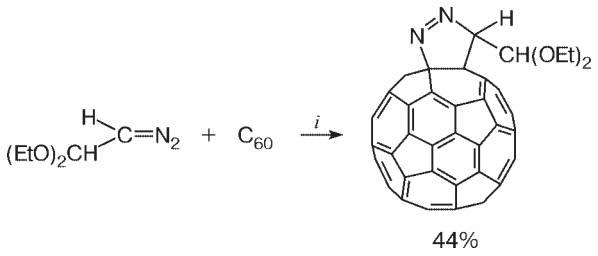
[2+3]-Cycloaddition of various 1,3-dipolar compounds is one of the most promising procedures for annelation of five-membered heterocyclic fragments to the C_{60} molecule. The ability of electron-deficient polyene C_{60} to act as a 1,3-dipolarophile was reported[68] for the first time at the symposium on the chemistry of large carbon clusters in 1992. The results of investigations on 1,3-dipolar cycloaddition to fullerene published up to 1997 were surveyed in the reviews.[1,3] Analysis of the results of recent investigations on the fullerene reactivity shows that the interest in this field of organic chemistry still persists.

2.1. Fullerenopyrazolines and fullerenotriazolines

As follows from the preceding section, many reactions of fullerene with diazo compounds or azides proceed through the initial 1,3-dipolar cycloaddition to form intermediate fullerenopyrazolines and fullerenotriazolines. Subsequent nitrogen elimination from these intermediates gives cyclopropanofullerenes and fullerenoaziridines, respectively, *i.e.*, adducts of these 1,3-dipolar cycloadditions appeared to be unstable. However, these intermediates can be isolated and characterized in some cases, *viz.*, under appropriate reaction conditions with the use of diazo compounds and azides possessing particular structures. For example, only one fullerenopyrazoline, *viz.*, the unsubstituted parent compound, was known before 1992.[69] Later on,[70] substituted fullerenopyrazoline was obtained in 44% yield by the reaction of fullerene with diethoxymethyldiazomethane under very mild conditions (tolu-

ene, 0 °C) (Scheme 32). The thermal transformation of this pyrazoline into isomeric methanofullerenes was also examined.

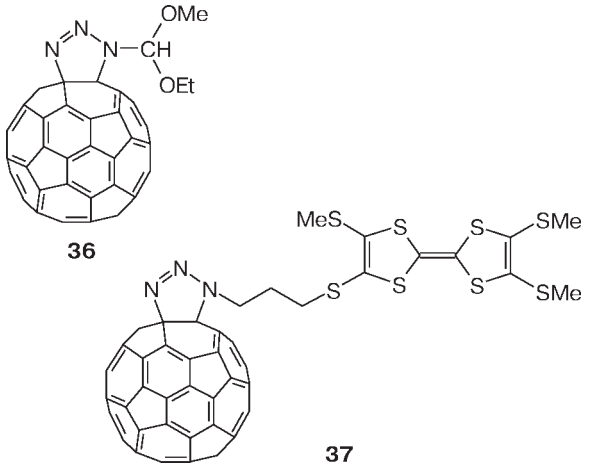
Scheme 32



i. Toluene, 0 °C.

The use of analogous methoxy(ethoxy)methyl azide led to stabilization of the corresponding triazoline **36**, which was generated by cycloaddition to [60]fullerene. This adduct is sufficiently stable that it was studied by X-ray diffraction analysis.[71] The new representative of donor-acceptor dyes, *viz.*, [60]fullerenotriazoline **37**, which was prepared from azide-containing tetrathiafulvalene,[72] also proved to be stable (Scheme 33).

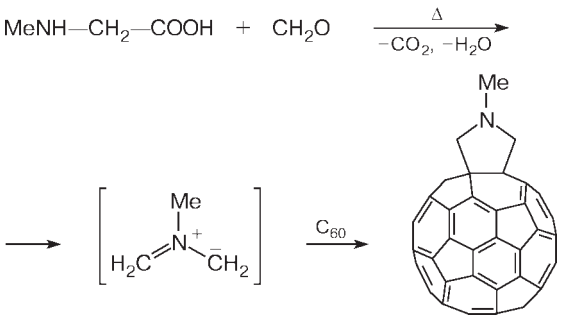
Scheme 33



2.2. Fullerenopyrrolidines

Of the convenient procedures for functionalization of C_{60} reported in recent years, the 1,3-dipolar cycloaddition of azomethine ylides finds most use. This reaction produces fullerenopyrrolidine (see, for example, Ref. 73). The most efficient procedure for generation of azomethine ylides involves decarboxylation of immonium salts prepared by condensation of α-amino acids with aldehydes (the Prato reaction). The simplest example is the reaction of *N*-methylglycine (sarcosine), formaldehyde, and C_{60} in refluxing toluene giving rise to *N*-methylfullerenopyrrolidine in 82% yield (Scheme 34).

Scheme 34



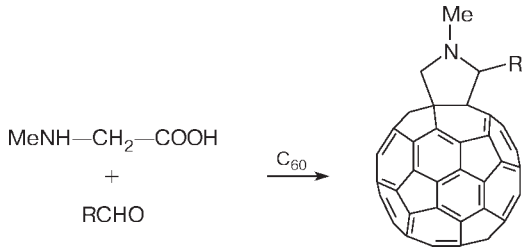
The main advantages of this reaction are as follows:

1) the reactions afford individual [6,6]-closed isomers;

2) α-amino acids and aldehydes or ketones (ketones can also be involved in these reactions) are commercially available or can be easily prepared from readily accessible precursors;

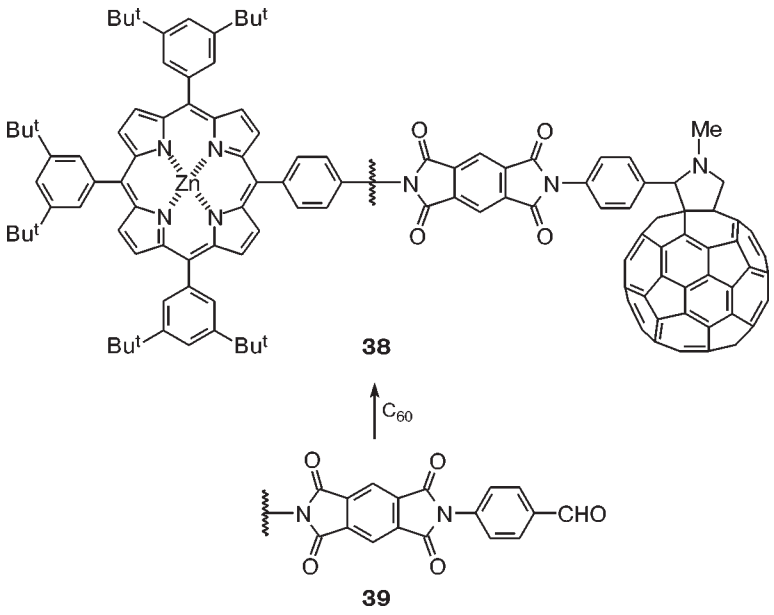
3) two substituents can simultaneously be inserted into the pyrrolidine ring (Scheme 35).

Scheme 35



In recent years, the functionalization of the fullerene sphere based on the Prato reaction has occupied a prominent place in the target-directed synthesis of fullerene derivatives for the design of new materials and potential biologically active compounds. The availability of a wide diversity of aldehydes allows one to synthesize a broad range of diad and triad donor-acceptor dyes according to the above-described procedure and to study their photophysical and electrochemical properties. Usually, these dyes involve the porphyrin fragment as the donor component and the fullerene chromophore serving as the acceptor, which are covalently linked by spacers of different nature. Generally, these systems are synthesized with the aim of modeling the processes of electron or energy transfer in the course of photosynthesis. For example, the study by electronic spectroscopy revealed the through-space interaction between the fullerene and tetraphenylporphyrin

Scheme 36



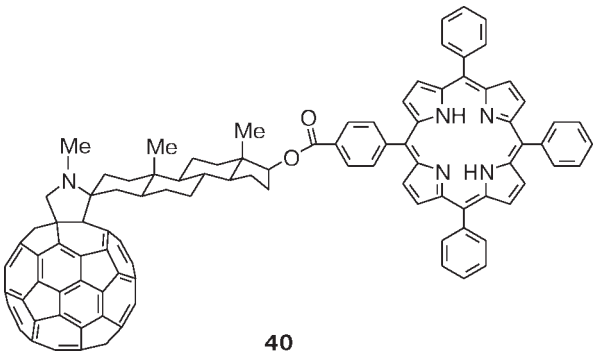
chromophores, which are covalently linked through the pyrrolidine ring.[74] This model compound was prepared by the Prato reaction from the corresponding porphyrin containing aldehyde function.

Efficient quenching of porphyrin fluorescence was observed in triad **38**, which was synthesized from the corresponding aldehyde **39**, sarcosine, and C_{60}. This fact is indicative of the efficient interaction between the chromophores in the excited state[75] (Scheme 36).

Analogous triads containing the second arylporphyrin fragment instead of the pyromellitimide fragment were also prepared.[76,77]

The long-lived charge-separated state was photoinduced also in the triad, which was synthesized by a similar procedure and which contained the porphyrin fragment covalently linked to C_{60} through carotenoid polyene,[78,79] as well as in a number of related diads and triads.[80—83]

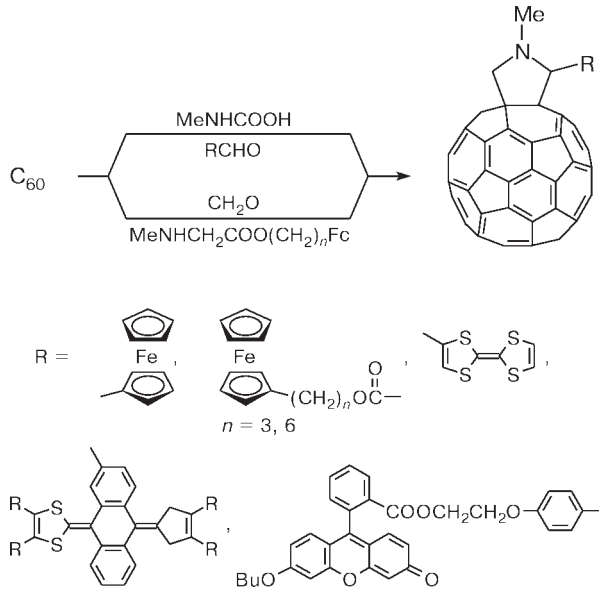
Steroid-linked porphyrin—fullerene hybrids, for example, compound **40**, have found application in photodynamic cancer therapy.[84]



40

The model photosynthetic antenna containing four covalently bound zinc tetraarylporphyrin fragments $(P_{ZP})_3$—P_{ZC} was attached to the free fullerene—porphyrin base (P—C_{60}) to form the $(P_{ZP})_3$—P_{ZC}—P—C_{60} hexad, which simulates the major functions of a complex natural photosynthetic center. This structure was also synthesized according to the sarcosine Prato method.[85] The ferrocene-porphyrin-fullerene triad was synthesized and its properties were examined for analogous purposes.[86]

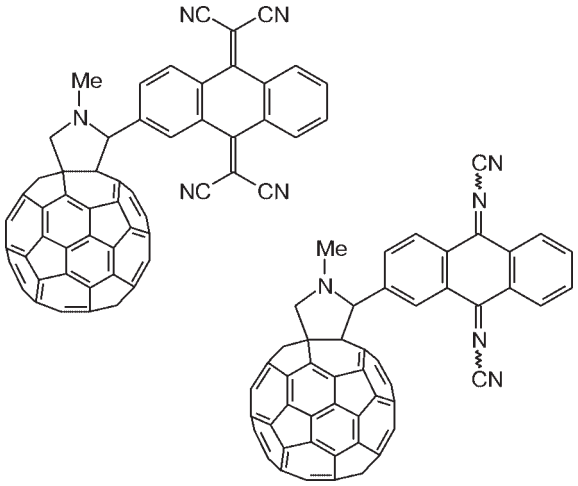
Scheme 37



Fc is ferrocenyl.

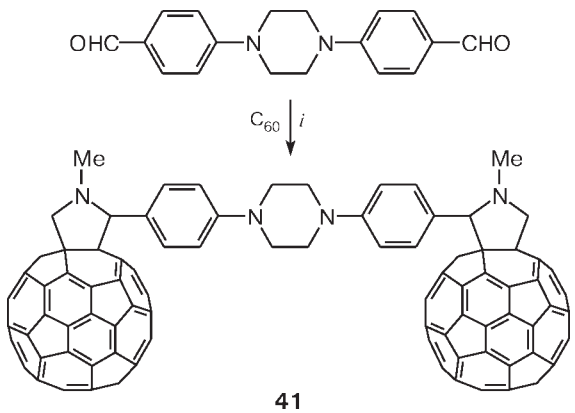
In the donor-acceptor complexes based on [60]fullerene, fragments of aniline,[87] ferrocene, tetrathiafulvalene,[88–96] fluoresceine,[97] and oligothiophene[98] were also used as the donor component (Scheme 37). In this case, the availability of a wide diversity of aldehydes RCHO also provides the successful application of the Prato reaction to the synthesis of model structures for the purpose of performing systematic studies of the electrochemical properties of fullerene derivatives containing additional donor or acceptor substituents.

With the aim of applying the sarcosine method to the synthesis of compounds possessing stronger electron-withdrawing properties as compared to fullerene by itself, the tetracyanoquinodimethane (TCNQ) and dicyanoquinonimine (DCNQ) fragments were attached to fullerene. These new fullerene derivatives are precursors suitable for the synthesis of intermolecular charge-transfer complexes.[99–101]



The dumbbell-like molecule containing two fullerene fragments was prepared from the corresponding dialdehyde.[102] The resulting dimer **41** is very poorly soluble in organic solvents (Scheme 38).

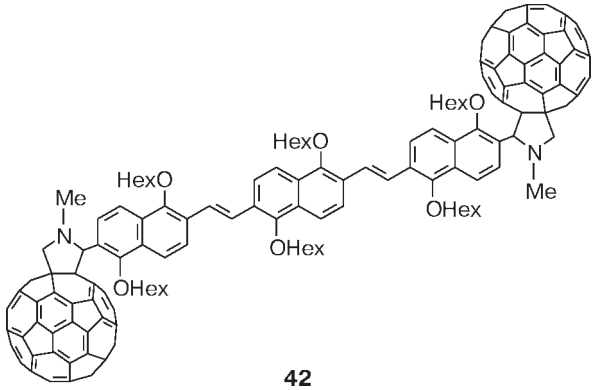
Scheme 38



41

i. $MeNHCH_2COOH$, toluene, 110 °C.

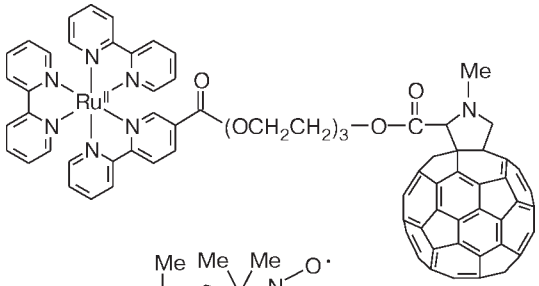
To the contrary, analogous compounds **42** bearing the oligo-2,6-naphthalenevinylene spacer, which were derived from fluorescent di(formyl)-oligo-2,6-naphthalenevinylenes, sarcosine, and C_{60}, are higly soluble. Since the carbon atom of the pyrrolidine ring is asymmetric, this compound was obtained as a mixture of rac- and *meso* forms in a total yield of 20%. In these triads, efficient quenching of fluorescence of the oligonaphthalenevinylene moiety was observed, which is indicative of the fast photoinduced electron transfer from the excited state of the oligomer to C_{60}.[103]



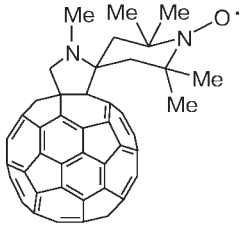
42

Hex = *n*-C_6H_{13}

The broad synthetic scope of the Prato reaction can also be demonstrated by the attachment of the oligophenylenevinyl fragments, which are covalently linked to the fullerene spheroid through the fused *N*-methylpyrrolidine ring,[104,105] peripheral branched polyaryl ethers containing the triethyleneglycol spacers (fullerene dendrimers),[106] calixarenes,[107] the Ru^{II} porphyrin complex,[108] the Ru^{II} tris(bipyridyl) complex (compound **43**),[109] and nitroxyl derivatives of C_{60} (**44**).[110]

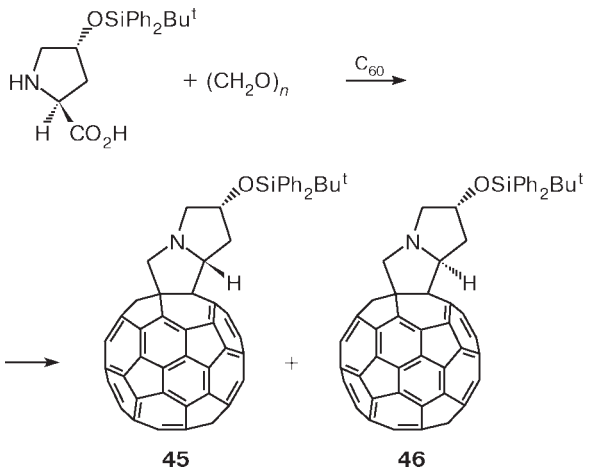


43



44

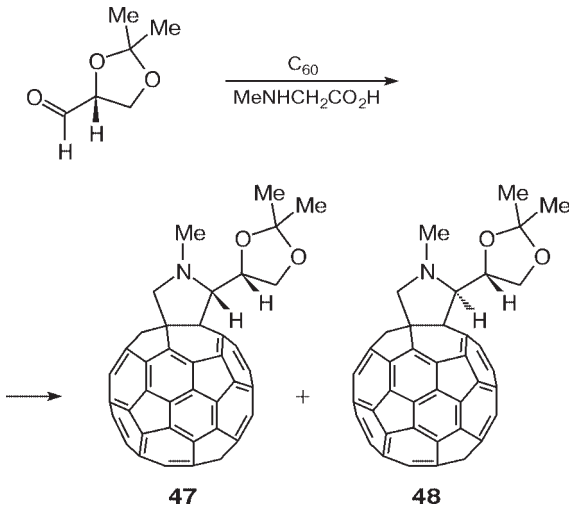
Scheme 39



1,3-Dipolar cycloaddition of chiral azomethine ylides is of interest by itself because it allows one to prepare disymmetric compounds with unusual chirality of the π-system of fullerene. The approach to these chiral structures is based on the use of chiral aldehydes or chiral amino acids in the sarcosine method.[111] Thus, the reaction of *O*-substituted (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (L-4-hydroxyproline), formaldehyde, and C_{60} in refluxing toluene afforded two diastereomeric monoadducts **45** and **46** in 11 and 24% yields, respectively (Scheme 39).

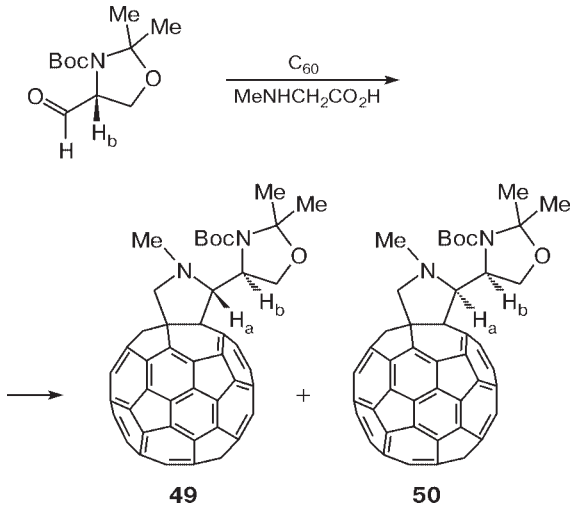
In situ condensation of the commercially available (+)-2,3-*O*-isopropylidene-D-glyceraldehyde with sarcosine in refluxing toluene afforded chiral azomethine ylide. The addition of the latter to C_{60} gave two diastereomeric fullerenopyrrolidines **47** and **48** in 5 and 17% yields, respectively[112] (Scheme 40).

Scheme 40



Enantiomerically pure Garner aldehyde (*tert*-butyl (*S*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate) is also a commercially available reagent. Unlike the above-described compound, this reagent possesses the chiral center with the *S* configuration and, hence, the Prato reaction of the latter compound with C_{60} would be expected to give the diastereomers in a reverse ratio. Actually, the ratio between diastereomeric monoadducts **49** and **50** was 86 : 14 (Scheme 41).[111]

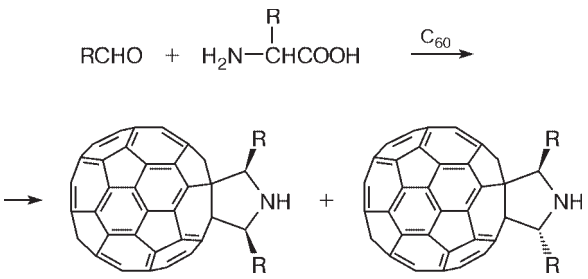
Scheme 41



The authors believed that steric effects are responsible for the stereoselectivity of cycloaddition in these reactions.

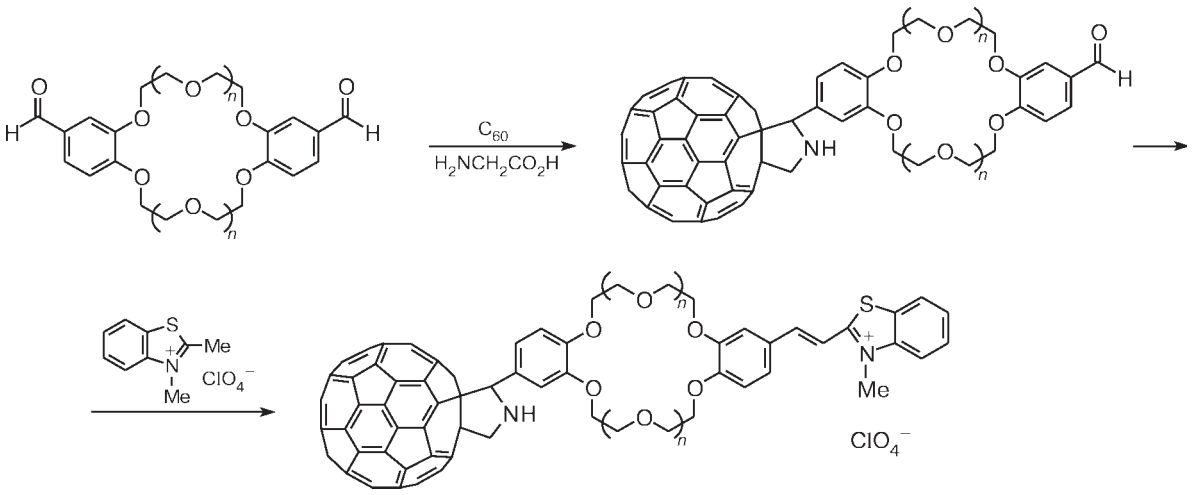
Analogous generation of 1,3-dipoles using *N*-unsubstituted amino acids instead of sarcosine gave rise to *N*-unsubstituted fullerenopyrrolidines whose functiona-

Scheme 42



R	Yield (%)	Ratio *trans* : *cis*
Me	20	5.5 : 7.4
Pr^i	23	—
Bu^i	15	13.8 : 20.2
Ph	35	—
CH_2Ph	28	13.0 : 17.6

Scheme 43



lization at the nitrogen atom opens up new synthetic possibilities. For example, this procedure was employed for the preparation of a series of 2,5-disubstituted fullerenopyrrolidines[112] (Scheme 42).

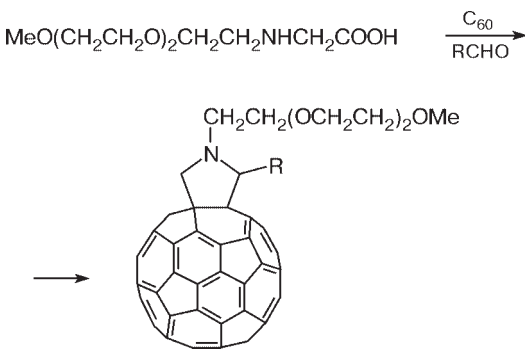
The *trans-d*,*l* isomers were separated through the formation of diastereomeric ureas by the reaction with chiral isocyanate. It is known that the nucleophilicity of the nitrogen atom in fullerenopyrrolidines is lower than that in pyrrolidines by itself.[113] Steric effects of the substituents at positions 2 and 5 lead to a further decrease in reactivity, however, isocyanates smoothly react with these fullerenopyrrolidines thus providing successful resolution. The absolute configurations of the C_2-symmetrical *trans*-isomers was established based on the circular dichroism spectra.

Condensation of C_{60} with glycine and bis(4-formylbenzo)-18-crown-6 or bis(4-formylbenzo)-24-crown-8 afforded new supramolecular dyes[114] (Scheme 43).

The Prato reaction with *N*-substituted glycines allowed the target-directed synthesis of fullerene derivatives possessing the desired properties. For example, this method was used for the preparation of water-soluble "nicotinofullerene" derivatives as potent biologically active compounds[115] (Scheme 44).

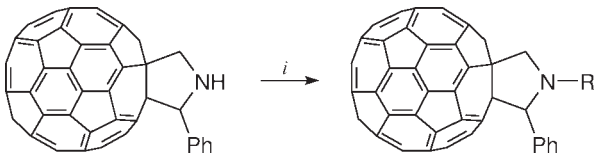
An alternative approach to *N*-substituted fullerenopyrrolidines is based on functionalization of NH-fullerenopyrrolidines.[113,115] Generally, it is hindered because of low reactivity of these compounds due to the influence of the fullerene core. However, these difficulties were successfully overcome with the use of, for example, alkylation under the phase-transfer conditions and microwave irradiation (MW)[116] (Scheme 45). By comparison, allylation in refluxing toluene during 24 h without microwave irradiation gave the corresponding product in only 16% yield.

Scheme 44



R = 3-Py, 4-Py, $CH_2(OCH_2CH_2)_2OMe$

Scheme 45

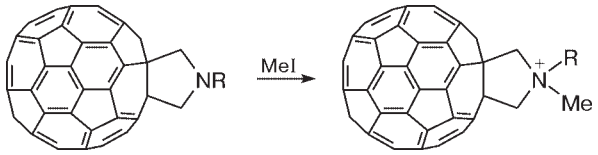


i. RBr, K_2CO_3, Bu_4NBr, MW, 10 min.

R = $PhCH_2$ (79%), 4-$NO_2C_6H_4CH_2$ (35%), 4-$MeO_2CC_6H_4CH_2$ (27%), *n*-C_8H_{17} (31%), $H_2C{=}CHCH_2$ (39%).

Various *N*-alkylfullerenopyrrolidines can be alkylated with iodomethane to form water-soluble quaternary salts possessing higher electron-withdrawing ability (according to the data from electrochemical studies) than fullerene by itself.[117,118] This was attributed to the inductive effect of the ammonium cation (Scheme 46).

Scheme 46

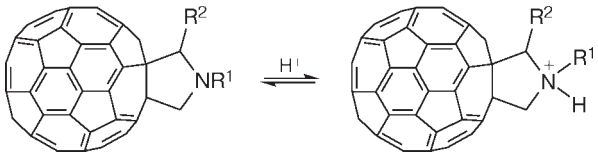


R = Me, $CH_2CH_2OCH_2CH_2OCOFc$

Fc is ferrocenyl.

Investigation of the acid-base equilibriums for 2-alkyl-NH-fullerenopyrrolidines and 2-alkyl-*N*-methylfullerenopyrrolidines demonstrated that the fusion of pyrrolidine with the fullerene core leads to an increase in acidity of the protonated nitrogen atom of the pyrrolidine moiety (pK_a are 6.3±0.1 and 7.5±0.1, respectively). In this case, the inductive effect is also primarily responsible for this increase in acidity. The acidity is only insignificantly dependent on the structural factors (the size of the radical R^2)[119] (Scheme 47).

Scheme 47



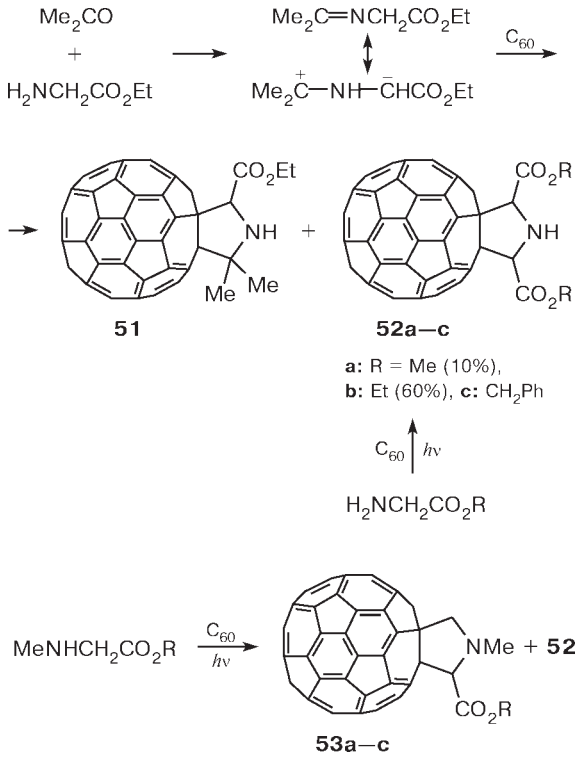
R^1 = H or Me, R^2 = Bu, C_8H_{17}, $C_{12}H_{25}$

N-Unsubstituted 2-arylfullerenopyrrolidines were also successfully arylated with 2,4-dinitrochlorobenzene under the phase-transfer conditions in 19—25% yields.[120] The use of 2,4-dinitrofluorobenzene in the presence of NaH for arylation of 2-phenylfullerenopyrrolidine made it possible to increase the yield up to 68%.[121]

Acylation of NH-fullerenopyrrolidine with Boc-protected alanine anhydride afforded fullerene-containing amino acid, which can be used in the subsequent peptide synthesis for the construction of a new dye containing the tris(bipyridyl) ruthenium complex at the terminus of the long peptide chain.[122]

The unexpected results were obtained in the reactions of C_{60} with esters of amino acids, different adducts being obtained under the conditions of thermolysis and photolysis.[123,124] Thus, the reaction of [60]fullerene with commercially available ethyl glycinate did not take place in the presence of acetone at room temperature, whereas 5-ethoxycarbonyl-2,2-dimethylfullerenopyrrolidine (**51**) was unexpectedly obtained along with a small amount of 2,5-diethoxycarbonylfullerenopyrrolidine (**52b**) upon refluxing in toluene (Scheme 48).

Scheme 48



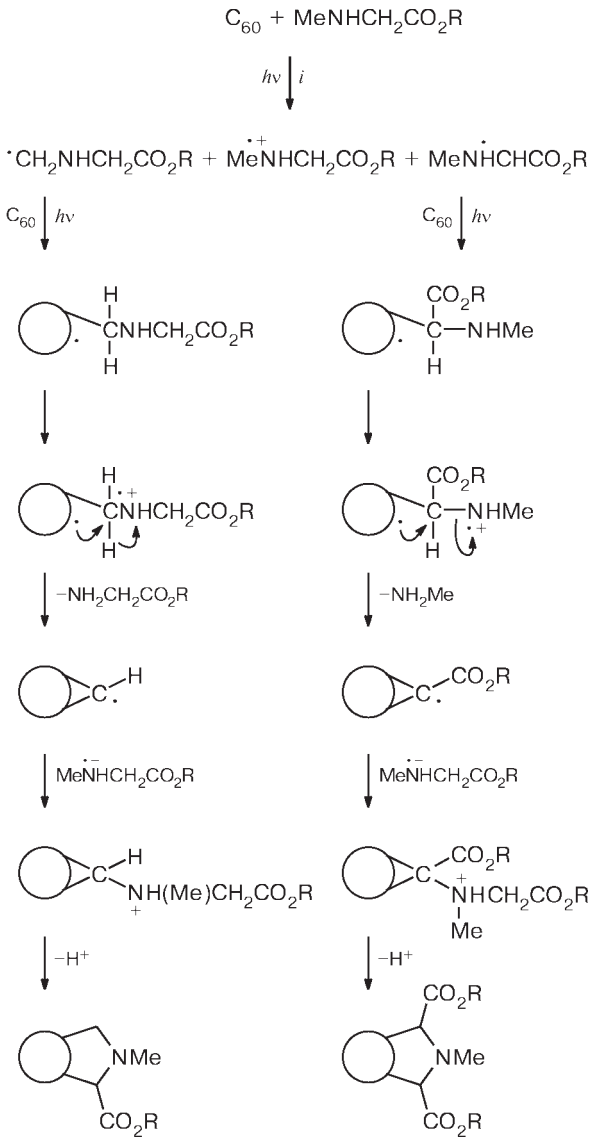
It was assumed that compound **51** was generated because the reaction mixture contained acetone, which formed a 1,3-dipole with ethyl glycinate (see Scheme 48). The mechanism of the photochemical process was proposed[123] (Scheme 49).

It is known that amines selectively generate radicals at the α-carbon atoms. Under irradiation, the formation of these radicals is promoted by singlet oxygen generated by C_{60} in very high yields.[125] Further transformation of these radicals is shown in the scheme based on the known radicalophile tendency of electrophilic fullerene. In spite of the multistep mechanism of this transformation, the photoreaction very efficiently afforded dicarboxylates **52** (rapidly and in high yields). Later on, an alternative approach to compound **52a** involving the addition of diester of iminodiacetic acid (Scheme 50) was extended to the reaction of fullerene with esters of polyaminocarboxylic acids, *viz.*, tetramethyl ethylenediaminotetraacetate and pentamethyl diethylenetriaminopentaacetate. This general process was systematically examined.[125]

The ability of aliphatic amines to selectively generate α-C-radicals was also demonstrated by radical cycloaddition of triethylamine to C_{60} to give *N*-ethyl-2,5-dimethylfullerenopyrrolidine[126,127] (Scheme 51).

This method was also used for the synthesis of a [60]fullerene derivative containing a fragment of alkaloid gramine[128] (Scheme 52).

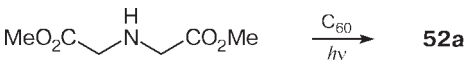
Scheme 49



i. Air.

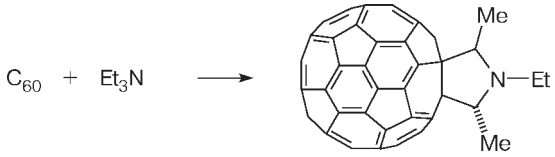
○ is the fullerene fragment.

Scheme 50

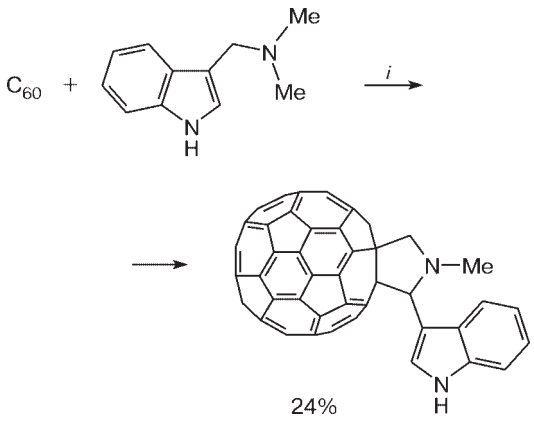


Even photoaddition of 3-diethylaminopropyne to C_{60} follows the same pathway in spite of the fact that one would expect the involvement of the triple bond in [2+2]-photocycloaddition (see Section 3).[129] Under these conditions, the corresponding 2-ethynylfullerenopyrrolidine was obtained in 25% yield (Scheme 53).

Scheme 51

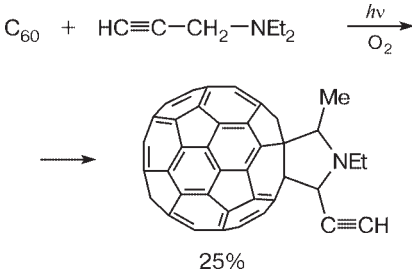


Scheme 52



i. *hν*, toluene, 20 °C.

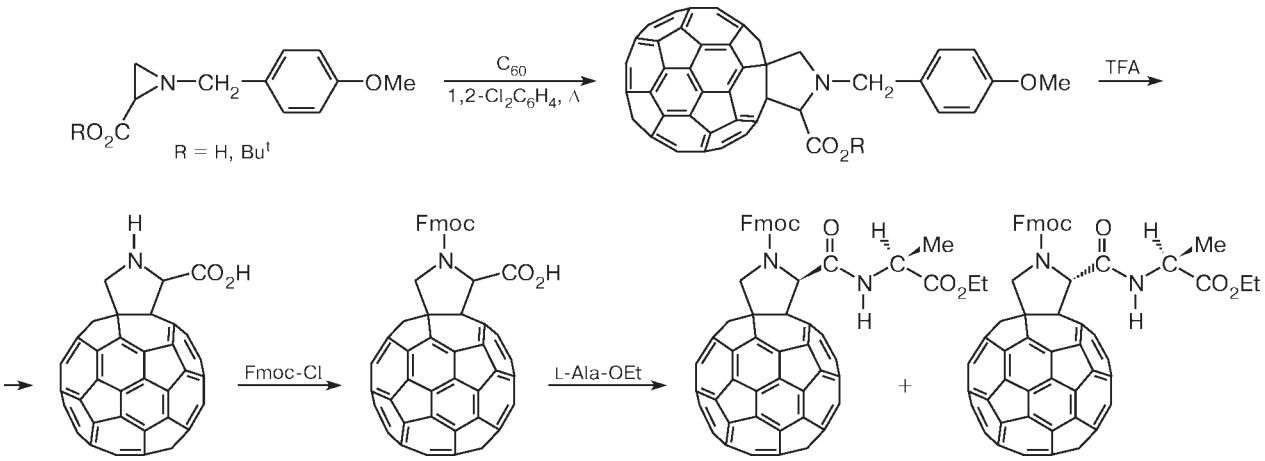
Scheme 53



Azomethine ylides can also be generated by thermal cleavage of aziridines. This approach (along with the Prato method) was applied to the synthesis of fullerenoproline derivatives.[130] A derivative of aziridinecarboxylic acid was used for the preparation of fullerene-containing peptides under standard conditions. The CD spectra of all optically active fullerene derivatives including fullerene-containing peptides (which were obtained by separation on chiral columns) have a characteristic absorption maximum at 428 nm, which is a diagnostic parameter for the determination of the absolute configuration of the α-carbon atom in the proline moiety. The calculated CD spectra confirmed the assignments made (Scheme 54).

An analogous method was used for the construction of a new support for HPLC based on [60]fullerene.[131] Thus, the thermal reaction of C_{60} with *N*-[3-(triethoxysilyl)pro-

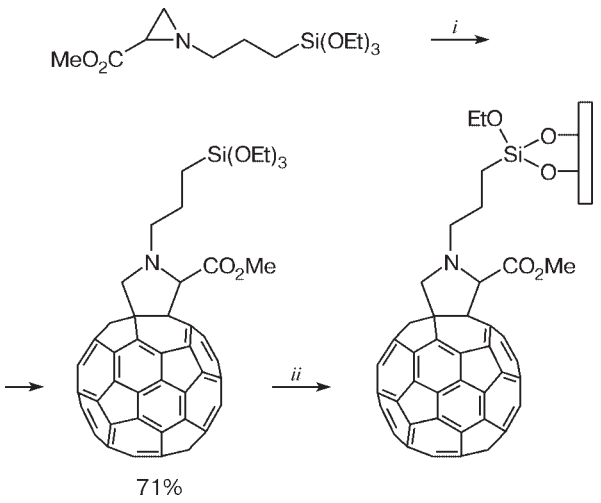
Scheme 54



Fmoc is 9-fluorenylmethoxycarbonyl.

pyl]-2-ethoxycarbonylaziridine afforded the corresponding fullerenopyrrolidine derivative, which was then anchored to silica gel. Such chromatographic materials are most advantageous for the separation of peptides bearing two peripheral ferrocene residues, which correspond to C_{60} in size (Scheme 55).

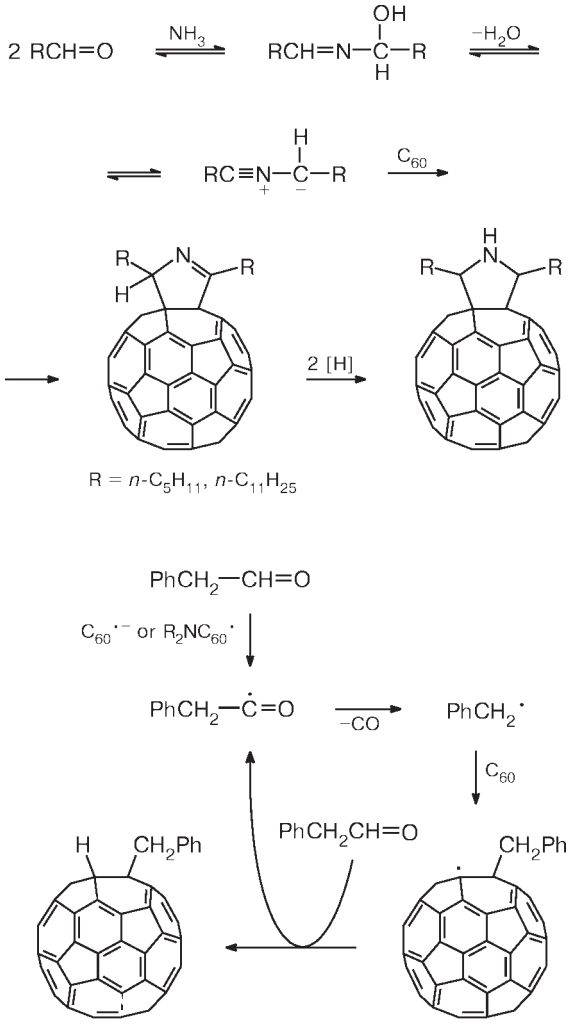
Scheme 55



Reagents and conditions: *i*. C_{60}, PhCl, Δ; *ii*. PhMe, Δ, silica gel.

Another synthetic approach to 2,5-dialkylfullerenopyrrolidines involves the reactions of C_{60} with aliphatic aldehydes in the presence of aqueous ammonia. The reaction of phenylacetaldehyde proceeded differently to form the product of hydrobenzylation of fullerene, conceivably, through decarbonylation.[132] The authors of the cited study proposed that the reaction mechanism in-

Scheme 56



volves the 1,3-dipolar cycloaddition in the step of formation of the pyrrolidine fragment, whereas the formation of the benzyl adduct follows the radical mechanism (Scheme 56).

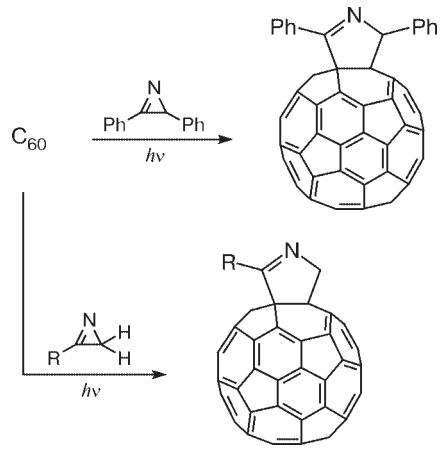
However, it should be noted that reduction of pyrrolines generated as an intermediate is a necessary step in the formation of pyrrolidines (see Section 2.3). Since no reducing agents were added to the reaction mixture, there are two possibilities: 1) the aldehyde serves also as the hydrogen donor or 2) its amine derivative acts as the electron donor.

2.3. Fullerenopyrrolines

Nitrile ylides serve as dipoles in 1,3-dipolar cycloaddition used for annelation of the pyrroline fragment with [60]fullerene. Several procedures were developed for the *in situ* generation of these active dipoles among which the photochemical cleavage of azirine derivatives is one of the most commonly used approach.[133,134] Thus, the photoreaction of C_{60} with a tenfold excess of 2,3-diphenylazirine afforded 1,3-diphenyl-3,3a-dihydro[60]fullereno[1,2-*c*]-3*H*-pyrrole (in 31% yield) along with polyaddition products.[134] Monosubstituted aryl-2*H*-azirines behave analogously[133] (Scheme 57).

In all the above-considered cases of fusion of five-membered heterocycles to the fullerene spheroid, only [6,6]-closed fullerene adducts were detected. However, it has recently been found for the first time that 1,3-dipolar cycloaddition of nitrile ylides to C_{60} can also produced [6,5]-open fulleroid isomers.[135] Actually, cycloaddition of nitrile ylide, which was generated *in situ* from *N*-benzyl-4-nitrophenylimidoyl chloride by treating with triethylamine, afforded [6,6]-closed 1-(4-nitrophenyl)-3-phenyl-3,3a-dihydro[60]fullereno[1,2-*c*]-3*H*-pyrrole (**54**) along with a mixture of diastereomeric [6,5]-open fulleroid cycloadducts **55a,b** in a ratio of 2 : 1. Besides, it was found

Scheme 57

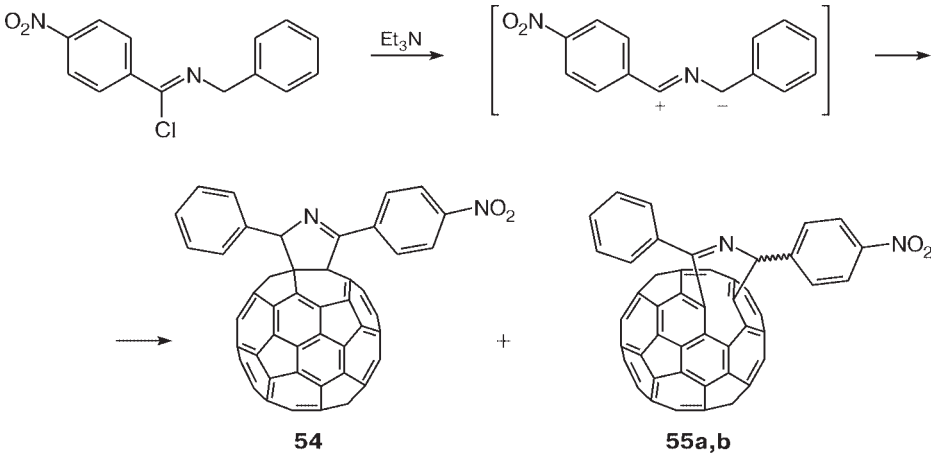


that the double bond in open cycloadducts **55a,b** is located in the α position with respect to the unsubstituted phenyl ring, whereas this bond in the [6,6]-closed isomer is in the α position with respect to the nitrophenyl substituent (Scheme 58).

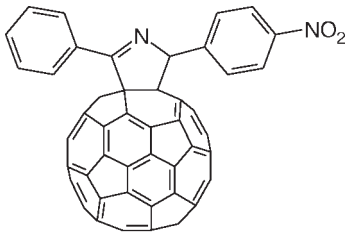
Interestingly, this reaction performed under milder conditions (in toluene at room temperature) afforded another set of cycloadducts.[127] In the latter case, the open isomers were not detected. The reaction mixture consisted of compound **54** and its isomer with respect to the double-bond location **56** along with the above-mentioned *N*-ethyl-2,5-dimethylfullerenopyrrolidine generated as a by-product in the radical reaction of triethylamine with fullerene.

Fullerenopyrrolines can be prepared not only by 1,3-dipolar cycloaddition of nitrile ylides to C_{60} but also by a fundamentally different approaches involving oxidative addition of methylene-active compounds. Recently,

Scheme 58



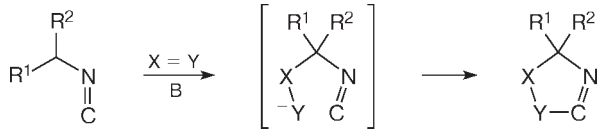
54 **55a,b**



56

isonitriles were used as such reagents.[136] The possibility of their use in these processes is associated with the ambiphile character of the terminal carbon atom of isonitrile. As a result, the latter can accept the anionic charge formed after the addition of the acid methylene function to the double bond of C_{60}. This approach assumes the nonconcerted mechanism of heterocyclization rather than the concerted 1,3-dipolar cycloaddition. Actually, it is known that the C=C and C=X bonds can be subjected to this type of cycloaddition to give various heterocycles including 1-pyrrolines (Scheme 59) (see the review[137]).

Scheme 59

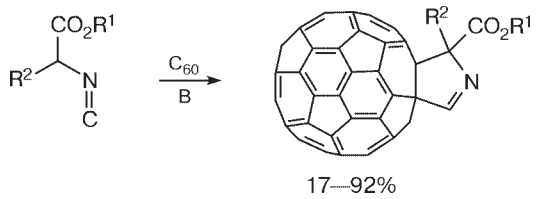


X, Y = C, N, O; B is a base.

The addition of isonitriles to C_{60} afforded fullerenopyrrolines (Scheme 60). The reaction with unsubstituted ethyl isocyanoacetate slowly proceeded even in the absence of a catalyst, but it is substantially accelerated in the presence of triethylamine. The use of DBU as a base is most efficient in the case of α-monosubstituted isocyanoacetates. Alternatively, Cu_2O can catalyze the cycloaddition of both activated and inactive isonitriles, such as $PhCH_2NC$.

Analogous oxidative cycloaddition of β-ketoesters and β-diketones to C_{60} resulted in annelation of the dihydrofuran fragment.[138] The authors believed that the process follows the concerted mechanism (Scheme 61).

Scheme 60

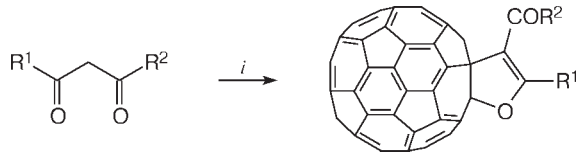


17—92%

R^1 = Me, Et, Bu^t; R^2 = H, Me, Pr^i, Bu^t, CH_2=CH—CH_2, $EtO_2C(CH_2)_3$

B is a base.

Scheme 61



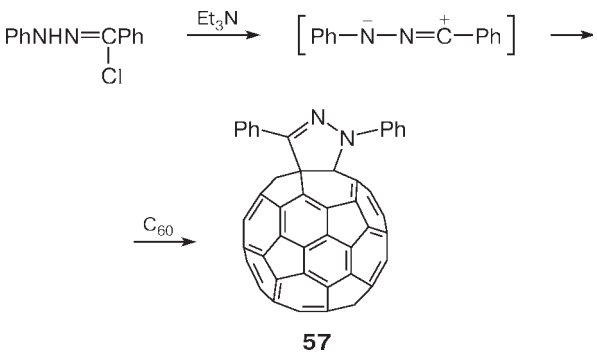
i. C_{60}/piperidine, PhCl, ~20 °C, 35 h.

R^1 = Me, R^2 = OBu^t (59%); R^1 = Me, R^2 = OEt (60%); R^1+R^2 = 2-O-C_6H_4O— (39%); R^1 = CH_2CO_2Me, R^2 = OMe (27%); R^1 = R^2 = Me (48%); R^1+R^2 = —$(CH_2)_3$—

2.4. Fullerenopyrazolines

Unlike the addition of diazoalkanes producing unstable adducts, which decompose further with nitrogen elimination to give the corresponding methanofullerenes (see Section 1.1), 1,3-dipolar cycloaddition of 1,3-diphenylnitrilimine generated *in situ* from *N*-(α-chlorobenzylidene)-*N*′-phenylhydrazine under the action of triethylamine enables one to obtain a stable [6,6]-closed product of pyrazoline annelation **57** (Scheme 62).[139]

Scheme 62

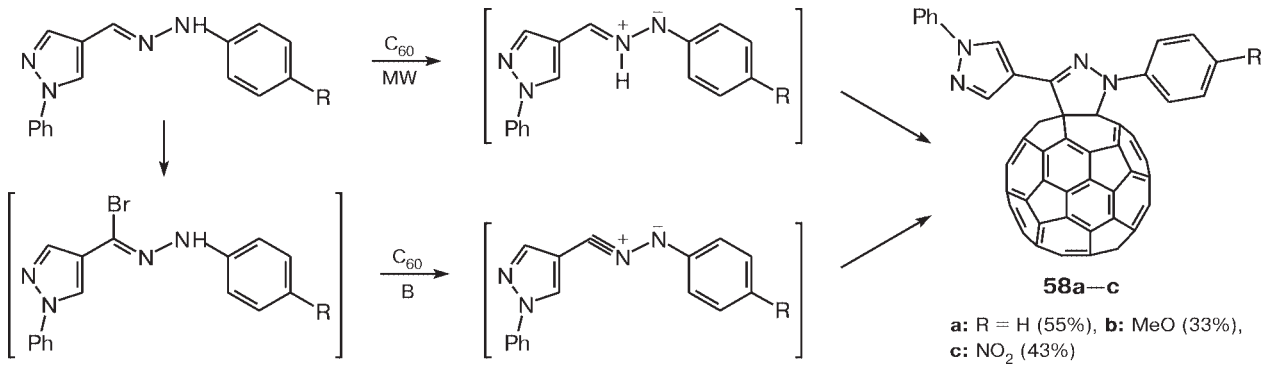


57

The electrochemical study of compound **57** revealed the intramolecular electron transfer.

An analogous charge transfer was observed in 1-aryl-3-(1-phenylpyrazol-4-yl)[60]fullereno[1,2-*d*]-2-pyrazolines **58a—c** prepared by two methods[140] (Scheme 63). One procedure is analogous to that described above with the only difference that nitrilimine is generated with the use of the corresponding hydrazonoyl bromide. An alternative procedure involves generation of the corresponding dipole from hydrazones under microwave irradiation. It should be noted that the latter process does not take place upon conventional heating.

Scheme 63

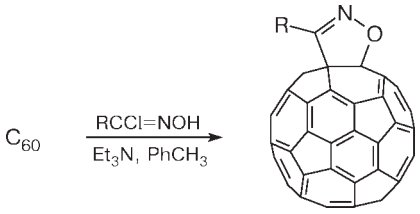


B is a base.

2.5. Fullerenoisoxazolines

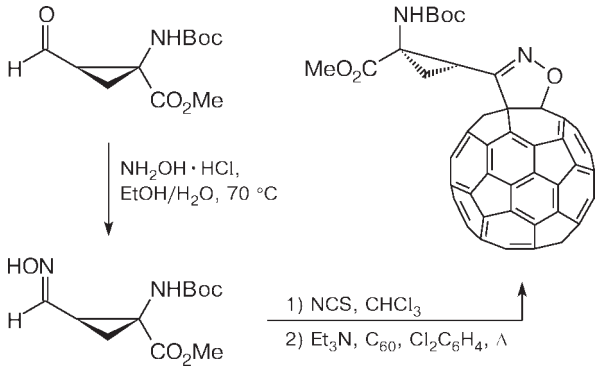
Fullerene C_{60} reacts with various nitrile oxides to form new C—C and C—O bonds, which provides an approach to a series of 6,6-fused fullerenoisoxazolines containing diversified substituents.[141—147] Since most of nitrile oxides are readily dimerized, they are usually generated *in situ* by various procedures, dehydrochlorination of hydroxymoyl chlorides with triethylamine or dehydrogenation of nitroalkanes being most generally employed (Scheme 64).

Scheme 64



The availability of oximes with various substituents offers considerable possibilities for functionalization of the fullerene spheroid. Thus, fullerenoisoxazolines containing either simple alkyl or very complex substituents R (the structures of many cycloadducts were established by X-ray diffraction analysis) were prepared: R = Me, Et, CO_2Et, $(CH_2)_4CO_2Me$, Ph, 4-C_6H_4OMe, 4-C_6H_4CHO;[141] CO_2CH_2Ph, CO_2Bu^t, 2,3,6,7-tetramethoxy-9-methoxycarbonylanthracen-10-yl;[142] $CH_2O(CH_2)_2O(CH_2)_2OMe$, 9-anthryl, COPh, 4-$C_6H_4OCH_2Ph$, CH_2COBu^t, $(CH_2)_2CO_2Me$, $(CH_2)_4NBocCH_2CO_2Bu^t$, 2,2-dimethyl-1,3-dioxolan-4-yl;[143] C_6F_5, pentafluorobiphenylyl;[144] isomeric *N*-phenylpyrazolyl;[148] 2-R´$SO_2C_6H_4$ (R´ = Ph, Bu^t, PhMeN)[149a]; R = $(Pr^iO)_2PO$;[149b] and *p*-benzoquinonyl.[101] The chiral cyclopropane-containing amino acid moiety was attached to the fullerene core according to the same scheme.[145] Since the configuration of the starting aldehyde is retained in the course of cycloaddition, the reaction afforded the first enantiomerically pure isoxazoline derivative of C_{60} (Scheme 65).

Scheme 65



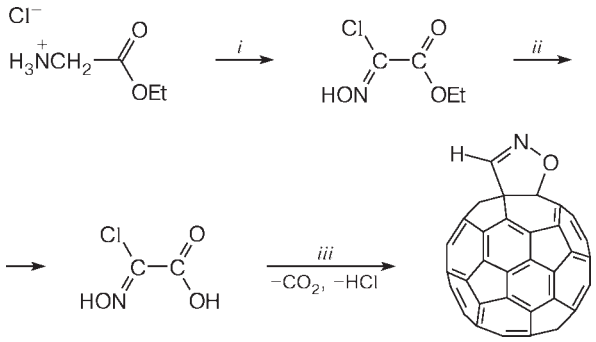
Unsubstituted [60]fullereno[1,2-*d*]isoxazoline was prepared by heating a mixture of C_{60} and chloroxyimidoacetic acid, which was apparently decomposed to fulminic acid in the course of the reaction[142] (Scheme 66).

3,3´-Bi([60]fullereno[1,2-*d*]isoxazole) was synthesized by double 1,3-dipolar cycloaddition of dicyane *N*,*N*´-dioxide to C_{60} (Scheme 67).[148]

Fullerene is readily involved in cycloaddition to *O*-trimethylsilyl nitronates generated upon treatment of nitroalkanes with a trimethylsilyl chloride —triethylamine system to give isoxazolines fused to C_{60} after the acid treatment[149a,150] (Scheme 68).

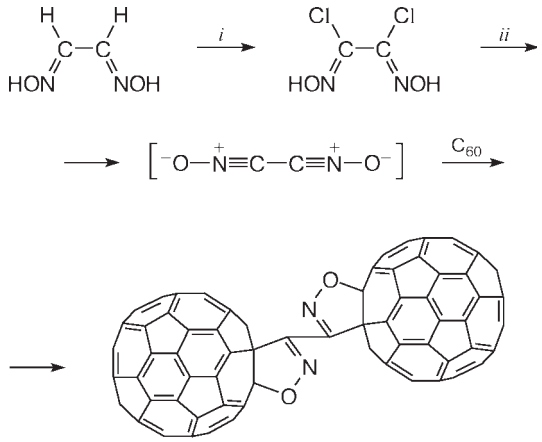
The basic cleavage of the N—O bond in unsubstituted fullerenoisoxazoline afforded 1-cyano-2-hydroxydihydro[60]fullerene,[151] whereas the corresponding silylated derivatives produced (under the analogous conditions) β-hydroxy(hydroxyimidoyl)dihydrofullerenes[149a] (Scheme 69).

Scheme 66



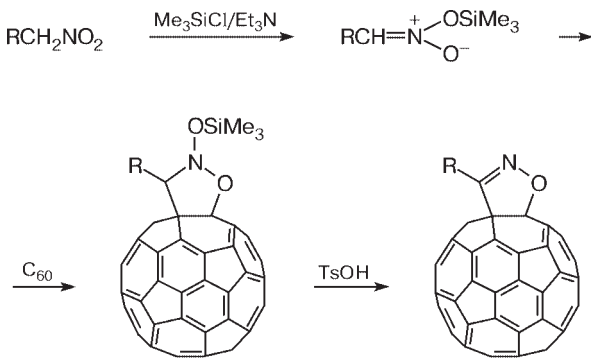
Reagents and conditions: *i*. $NaNO_2$/HCl, H_2O;
ii. HCl/ether, Δ; *iii*. C_{60}/toluene, 80 °C.

Scheme 67



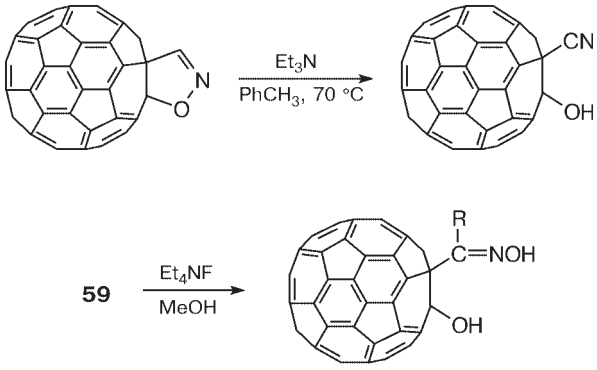
Reagents and conditions: *i*. Cl_2/0 °C, H_2O;
ii. Na_2CO_3, H_2O/toluene.

Scheme 68



R = H (42%), CH_2OH (30%), $(CH_2)_2CO_2Et$ (42%), $(CH_2)_2CN$ (31%), $(CH_2)_2COMe$ (22%)

Scheme 69

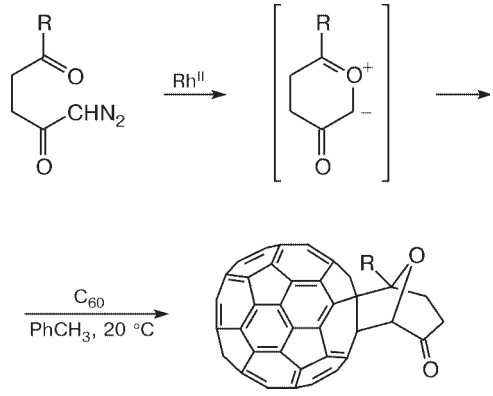


R = Me (65%), $(CH_2)_2CO_2Et$ (45%)

2.6. 1,3-Dipolar cycloaddition of carbonyl and thiocarbonyl ylides

Being versatile 1,3-dipoles, carbonyl ylides react with C_{60} to produce a new class of cycloadducts as exemplified by the addition of six-membered carbonyl ylides generated by the Rh^{II}-catalyzed transformation of 1-diazo-5-R-pentane-2,5-diones.[152] These reactions yielded the 8-oxabicyclo[3.2.1]octane system bearing the tetrahydrofuran fragment fused to the fullerene core (Scheme 70).

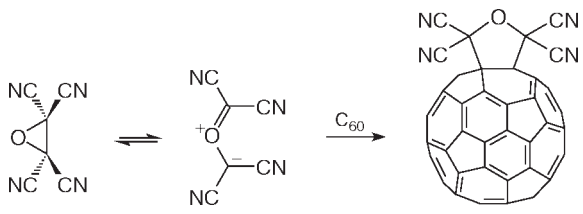
Scheme 70



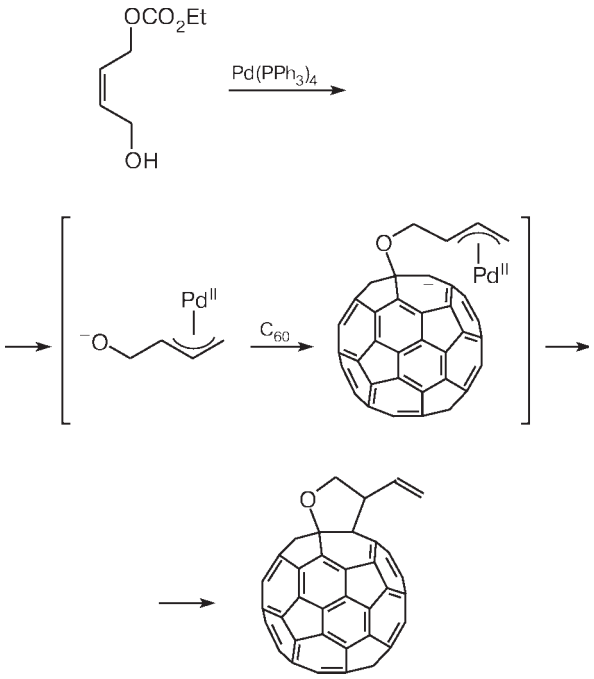
R = Ph (86%), Tol (87%), ferrocenyl (85%)

Another procedure for the preparation of the stable tetrahydrofuran adduct of fullerene is based on genera-

Scheme 71



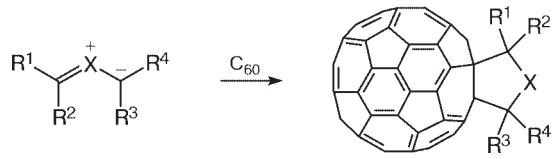
Scheme 72



tion of carbonyl ylide by the thermal (>100 °C) opening of tetracyanooxirane.[153] As opposed to the corresponding aromatic derivatives, this fullerenotetrahydrofuran is stable to elimination of $CO(CN)_2$ because of the absence of protons.

Palladium-catalyzed [2+3]-cycloaddition of *cis*-$HOCH_2CH{=}CHCH_2OCO_2Et$ to [60]fullerene produced the corresponding 2-vinyltetrahydrofuran adduct.[154] Although the mechanism of this process remains unclear, the authors believed that nucleophilic addition of π-allylpalladium alkoxide to C_{60} afforded the corresponding fullerene anion, which, in turn, nucleophilically attacked the π-allylpalladium system to give the above-mentioned tetrahydrofuran adduct (Scheme 72).

Scheme 73

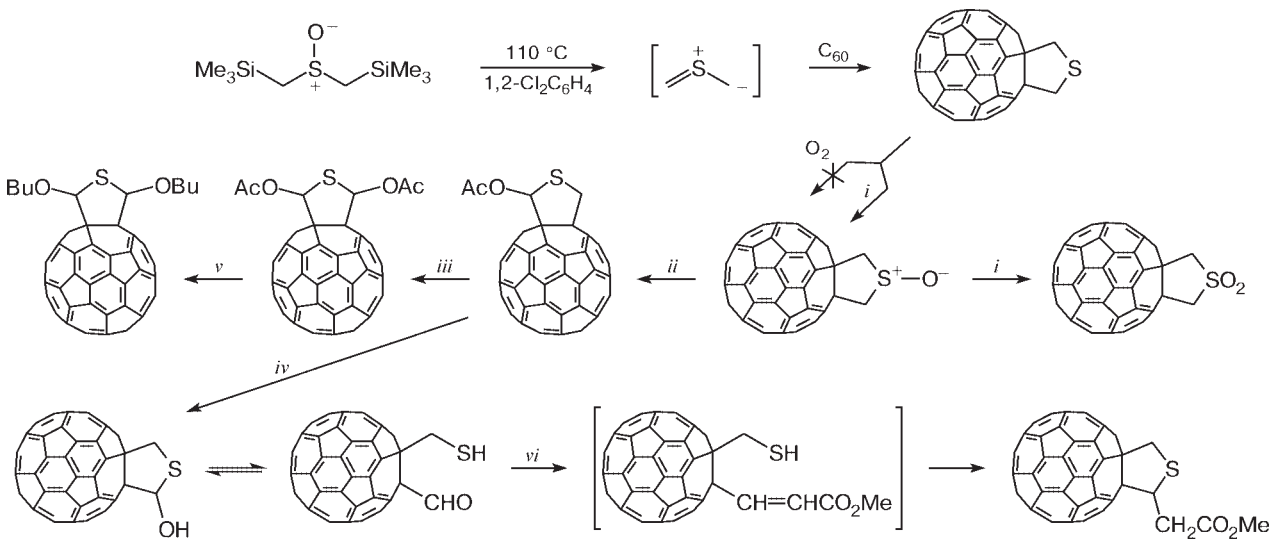


X = N, various R^1, R^2, R^3, R^4;
X = O, $R^1 = R^2 = R^3 = R^4$ = CN;
X = S, $R^1 = R^2 = R^3 = R^4$ = H

In the general case, the use of heteroylides for the synthesis of saturated five-membered heterocycles fused to [60]fullerene can be represented by Scheme 73.[155,156]

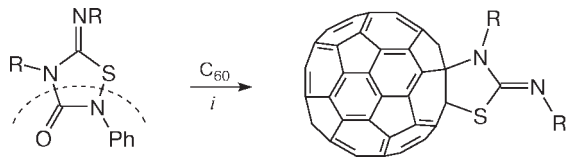
The annelation of the pyrrolidine ring (X = N, azomethine ylides), which is described in detail in the previous sections, has found a wide application, whereas, as far as we know, only two examples of annelation of the tetrahydrofuran ring (X = O, carbonyl ylides) are available in the literature.[153,154] The "sulfur version" (X = S, thiocarbonyl ylides) of this process remained unknown until 1999. The simplest thiocarbonyl ylide was generated for the first time by the thermal sila-Pummerer rearrangement of bis(trimethylsilylmethyl) sulfoxide.[155,156] This ylide smoothly added to C_{60} to produce fullerenotetra-

Scheme 74



Reagents and conditions: *i*. MCPBA; *ii*. Ac_2O, 110 °C; *iii*. 1) MCPBA, 2) Ac_2O; *iv*. H^+/H_2O or $Pr^i{}_2LiAlH_2$; *v*. BuOH, CSA. *vi*. $Ph_3P{=}CHCO_2Me$.

Scheme 75



i. Toluene, 110 °C, 24 h.

R = Ph (58%), Tol (71%), 4-BrC_6H_4 (46%), 4-ClC_6H_4 (31%), 4-$MeOC_6H_4$ (58%)

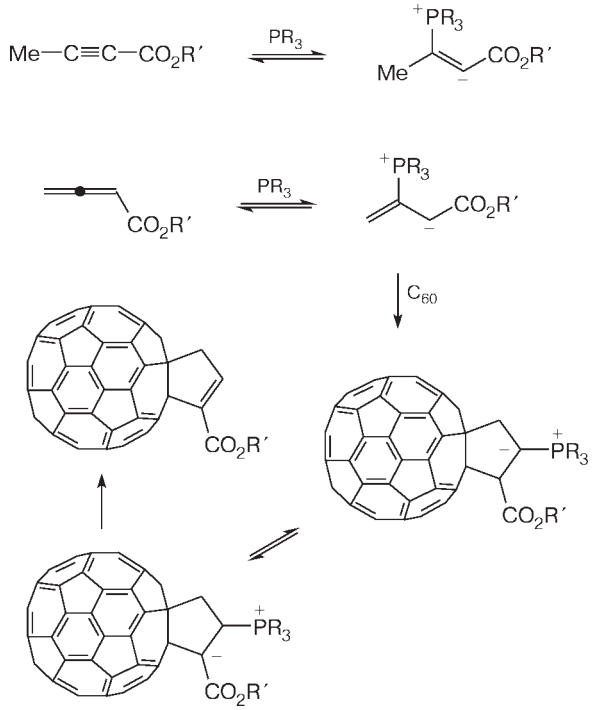
hydrothiophenes. Their high reactivity with respect to various chemical agents allows the insertion of the functional groups in the immediate vicinity of the fullerene spheroid. Examples of such chemical transformations are shown in Scheme 74.

Annelation of 2-imino-1,3-thiazolidine fragments with C_{60} can be carried out with the use of latent 1,3-dipoles, *viz.*, 5-imino-1,2,4-thiadiazolidin-3-ones, which generate the corresponding ylides upon thermal elimination of phenylisocyanate[157] (Scheme 75).

2.7. Cyclopentafullerenes

[2+3]-Cycloaddition allows annelation not only of heterocyclic but also of carbocyclic fragments with [60]fullerene. Thus, C_{60} reacted with esters of buta-2,3-dienoic acid and but-2-ynoic acid in the presence of phosphine catalysts to form the corresponding alkyl cyclopenta[60]fullerenecarboxylates.[158,159] The mechanism of this transformation is shown in Scheme 76.

Scheme 76

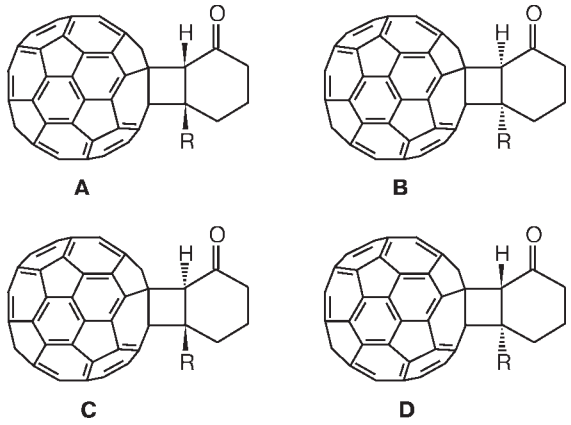


3. [2+2]-Cycloaddition

It is known that electrophilic [60]fullerene is prone to radical addition reactions. This property can be used for annelation of cyclobutane fragments with C_{60} through [2+2]-photocycloaddition. An example is photocycloaddition of cyclic enones to C_{60} (Scheme 77).[160]

Based on the fact that irradiation at the wavelength where only fullerene absorbs (λ = 532 nm) did not afford the C_{60}—enone adduct, the authors concluded that the reaction mechanism involves the addition of enone in the excited triplet state to fullerene in the ground state through the triplet biradical intermediate. It is seen from the above-mentioned Scheme **77** that bulky substituents in enones hinder photocycloaddition.

Stereoisomeric cyclobutanofullerenes (**A**—**D**) obtained by [2+2]-cycloaddition of cyclohexenone were separated by HPLC on a column with the Whelk-O chiral phase and their CD spectra were measured.[161]

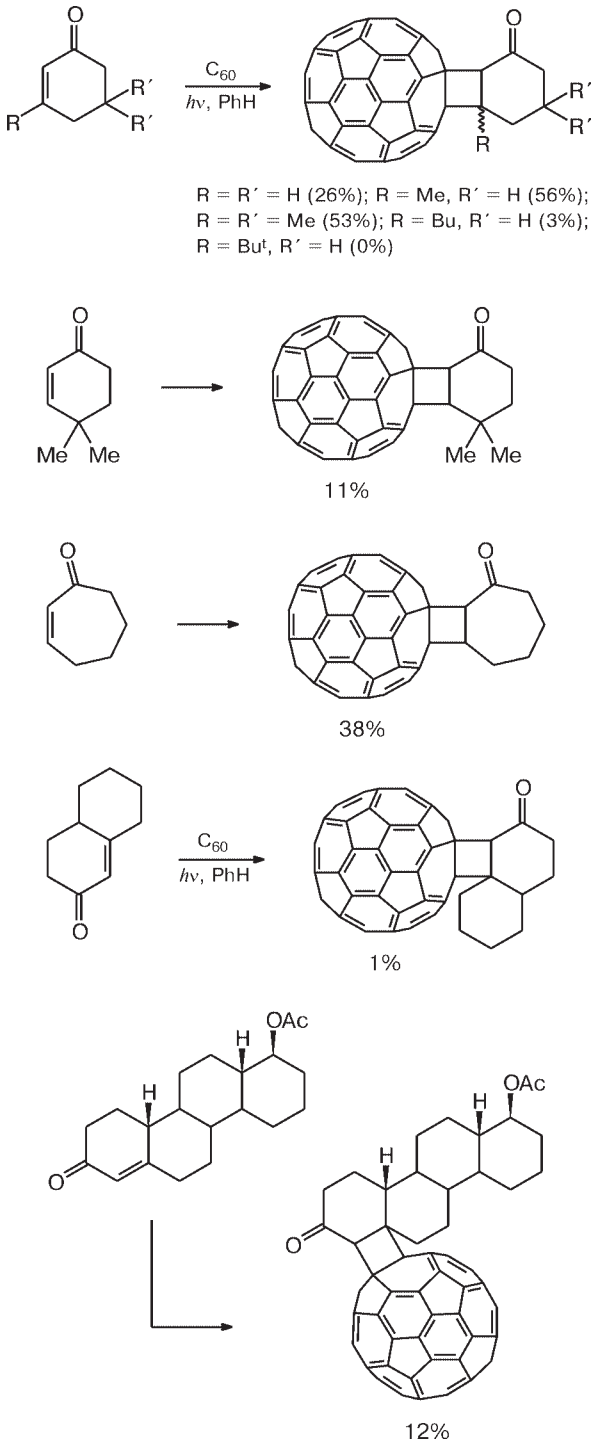


R = H, Me

Photocycloaddition of cyclic 1,3-diones or their trimethylsilyl derivatives to C_{60} also proceeds through cyclobutane intermediates, but these intermediates undergo further transformations producing finally two fused fullerenofurans, *viz.*, achiral **60** and chiral **61** [162] (Scheme 78).

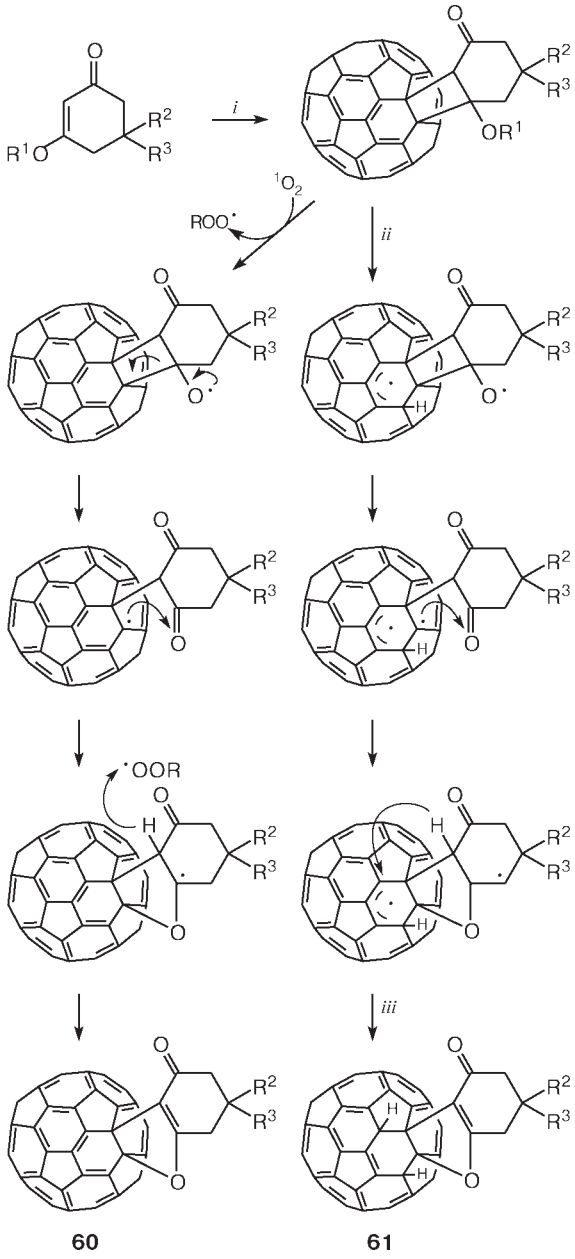
Electron-rich alkynes can also be involved in [2+2]-photocycloaddition to C_{60}. Thus, the addition of *N*-(4-methylpent-3-en-1-yn-1-yl)-*N*,*N*-diethylamine produced stable fused cyclobuteneamine **62**, which underwent further autosensitized photooxidation to form dihydrofullerenocarbamide **63** [163] (Scheme 79).

Scheme 77



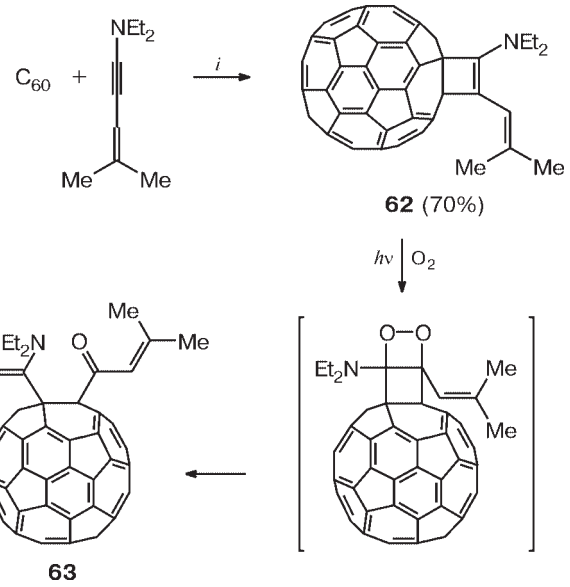
Examination of the stereochemistry and secondary isotope effects of [2+2]-photocycloaddition of *trans,trans*-, *cis,cis*-, and *cis,trans*-hexa-2,4-dienes, 2,5-dimethylhexa-2,4-diene, and their deuterated analogs to C_{60} demonstrated[164] that these reactions involve the addition of diene to C_{60} in the excited triplet state through electron transfer from diene followed by rapid collapse of the initially formed ion pair into the corresponding [2+2]-cycloadducts. The first reaction step giving rise to the biradical intermediate is rate-determining and is responsible for the observed regioselectivity and secondary isotope effects. The second step (collapse of ion pairs) determines the diastereoselectivity, with thermodynamically more stable *trans*-cyclobutane adducts predominat-

Scheme 78



Reagents and conditions: *i*. C_{60}, *h*ν, benzene; *ii*. 1) *h*ν, 2) intramolecular hydrogen abstraction; *iii*. 1,3-H shift.

Scheme 79



i. $h\nu$, >500 nm.

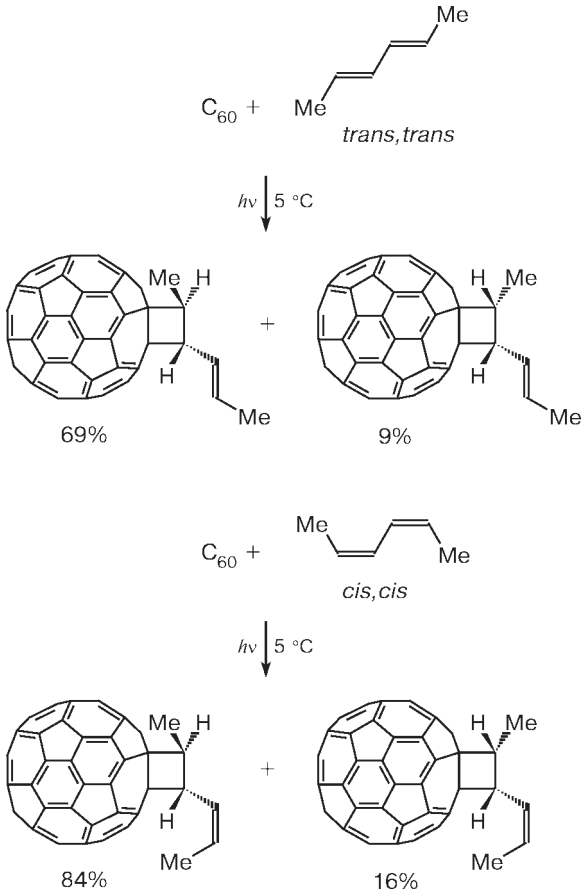
ing. It should be noted that the stereochemistry of the double bond of the initial diene involved in the reaction was lost in all cases, *i.e.*, *trans*-cyclobutanes were predominantly formed (Scheme 80). Apparently, this phenomenon results from the fact that the lifetime of the biradical intermediate is sufficiently large for rotation about the C(2)—C(3) bond to become possible resulting in the loss of the stereochemical purity of the addition. However, the stereochemistry of the double bond of diene, which is not involved in the reaction, is retained.

Analogous conclusions about the stepwise reaction mechanism giving rise to an open biradical or bipolar intermediate were made based on the study of the stereochemistry and the kinetic isotope effects of [2+2]-photocycloaddition of isomeric styrenes to C_{60}[165—167] (Scheme 81).

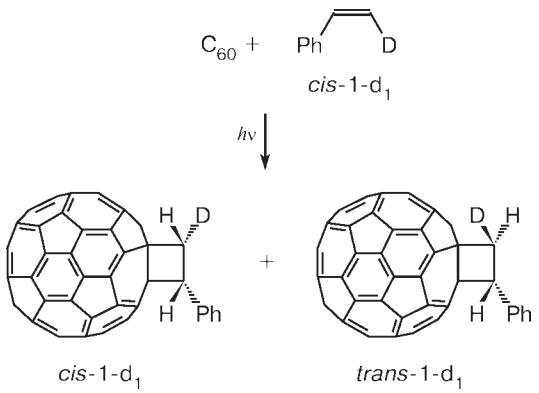
Acyclic enones also react with fullerene by the [2+2]-photocycloaddition mechanism.[168] Thus, irradiation of a mixture of C_{60} with a 1000-excess of mesityl oxide for 30 min afforded the corresponding [2+2]-cycloadduct. However, this reaction was reversible and its equilibrium constant was very low (Scheme 82).

The photochemical addition of dienones, *viz.*, *trans*-6-methylhepta-3,5-dien-2-one (**64**) and *trans*-2-methylhepta-2,5-dien-4-one (**65**)[168] (Schemes 83 and 84, respectively), was studied with the aim of elucidating the regio- and stereoselectivity of this reaction. These dienones are ideally suited for these purposes because compound **64** contains two nonequivalent substituted conjugated double bonds both of which can be involved in [2+2]-cycloaddition. On the other hand, two sterically and electronically nonequivalent double bonds in the

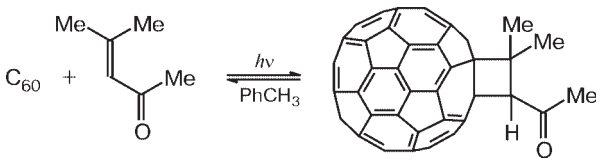
Scheme 80



Scheme 81

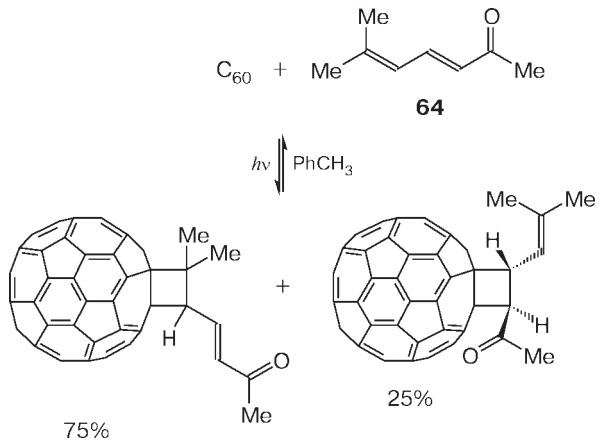


Scheme 82

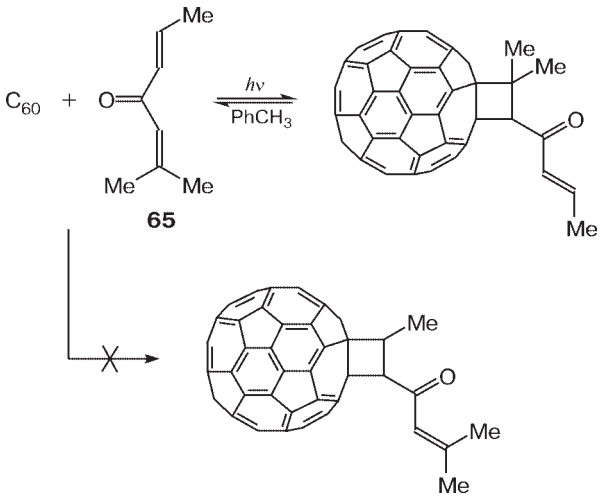


dienone fragment of compound **65** are separated by the carbonyl group. In the case of dienones **64** and **65**, the equilibrium of cycloaddition is shifted toward the adducts to a greater extent than in the case of mesityl oxide. Cycloaddition of dienone **64** produced two regioisomers in a ratio of 3 : 1 (see Scheme 83).

Scheme 83



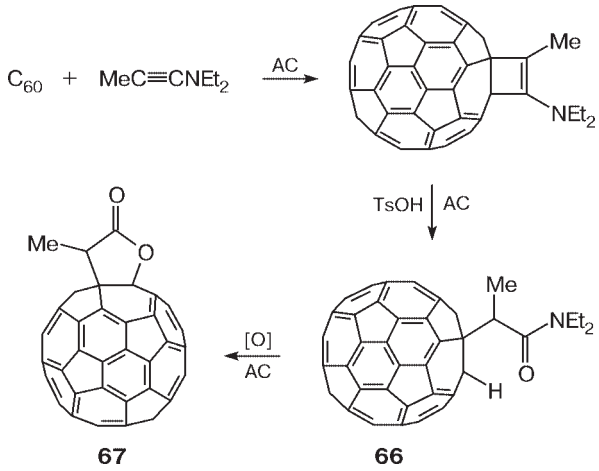
Scheme 84



Photocycloaddition of dienone **65** proceeded regiospecifically only at the more substituted double bond (see Scheme 84).

Acetylenes can be involved both in photochemical and thermal [2+2]-cycloaddition to C_{60}. Thus, the reaction of fullerene with diethylaminopropyne afforded the cyclobutene adduct, which underwent quantitative hydrolysis to give amide **66**.[169] Oxidative cyclization of this amide on charcoal (other catalysts proved to be inefficient) produced new fullerene lactone **67** (Scheme 85).

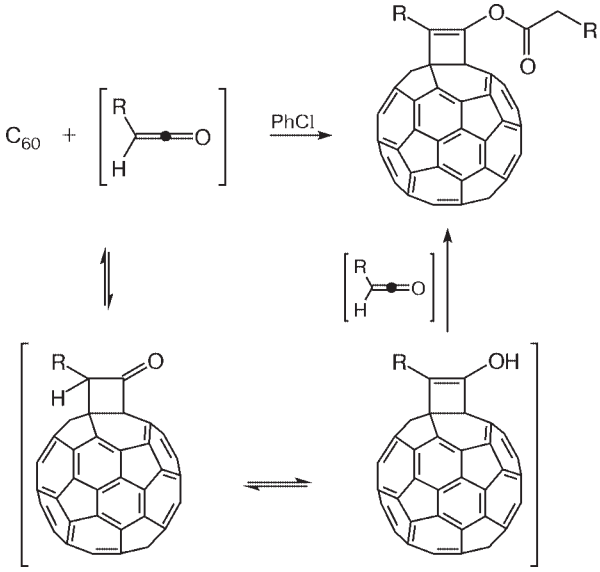
Scheme 85



AC is activated charcoal.

[60]Fullerene reacts with aryloxy- and alkoxyketenes generated *in situ* from the corresponding acid chlorides and triethylamine to form 1:2 adducts in good yields.[170] The reactions proceeded through the formal [2+2]-cycloaddition followed by enolization and acylation of the initially formed 1:1 cycloadduct (Scheme 86).

Scheme 86

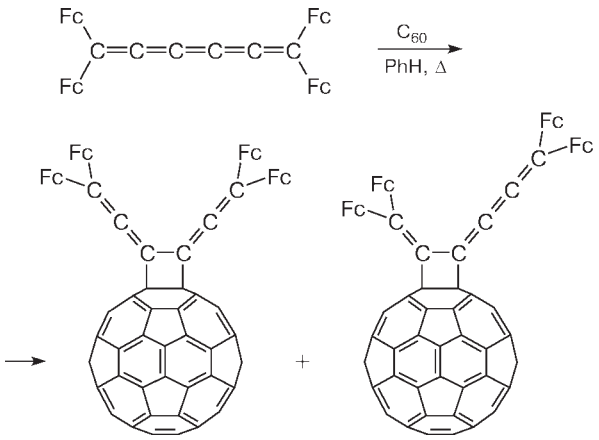


R = PhO (61%), *p*-ClC_6H_4O (39%), $PhCH_2O$ (58%), EtO (58%), MeO (37%)

Cycloaddition of tetraferrocenyl[5]cumulene to [60]fullerene upon refluxing in benzene afforded a mixture of regioisomeric [2+2]-cycloadducts[171] (Scheme 87).

[2+2]-Cycloaddition of dehydrobenzene, which was generated from 4,5-dimethoxyanthranilic acid, to fulle-

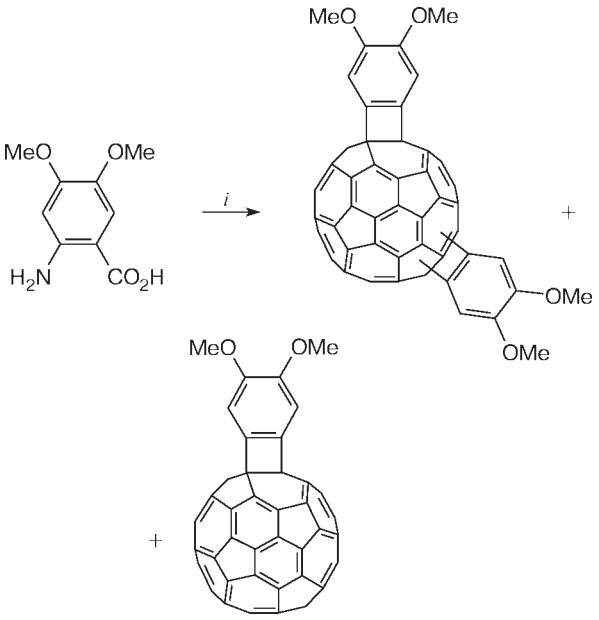
Scheme 87



Fc is ferrocenyl.

rene produced a mixture of mono- and bis-adducts[172] (Scheme 88).

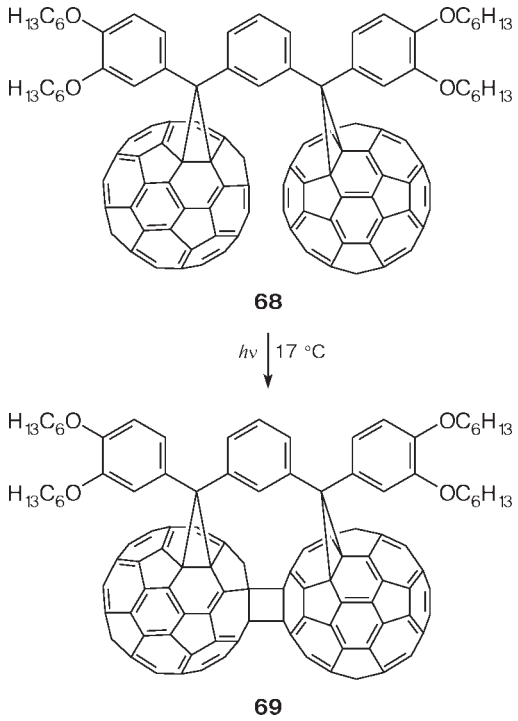
Scheme 88



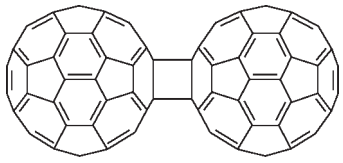
i. C_{60}, *i*-$C_5H_{11}ONO$, toluene, Δ.

In studies of [2+2]-cycloaddition reactions, considerable recent attention has been focused on the possibility of the use of this procedure for the preparation of fullerene dimers. For example, photodimerization of readily soluble *m*-phenylenebis(arylmethanofullerene) **68** bearing the fullerene fragments in close proximity to each other gave rise to dimer **69** in high yield (84%)[173] (Scheme 89).

Scheme 89



Contraction of the crystal of the $(ET)_2C_{60}$ complex (ET is bis(ethylenedithio)tetrathiafulvalene) at 5 GPa and 200 °C produced the fullerene dimer C_{120} in ~80% yield.[174] In this case, pressure-initiated cross-coupling of fullerene molecules is promoted by the close packing in the crystal. The C_{120} dimer readily dissociates into two C_{60} molecules upon heating, vibration grinding, exposition to visible light, or electrochemical reduction.

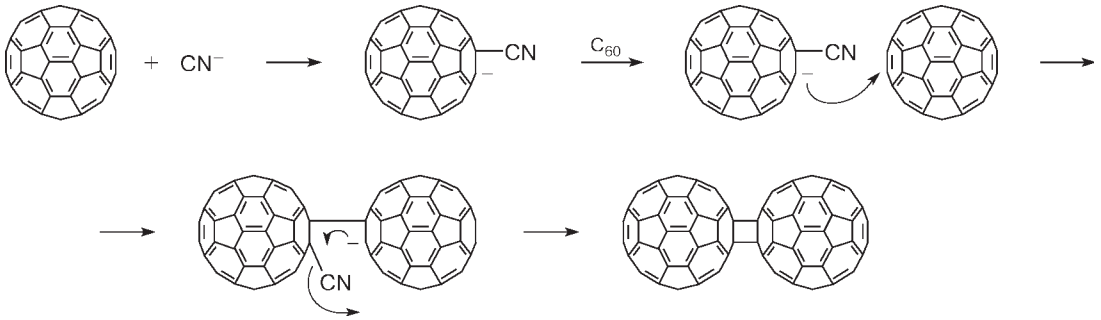


C_{120}

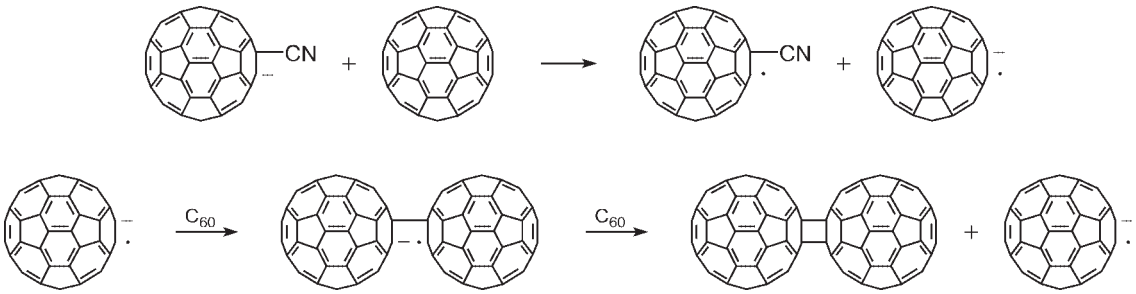
This dimer was synthesized[175] in large amounts by the mechanochemical reaction of C_{60} with KCN using a high-speed vibrating mill. Under optimum conditions, the reaction produced only the dimer. In the final mixture, this dimer and unconsumed fullerene are present in a ratio of 3 : 7. Two possible mechanisms of this reaction were proposed (Schemes 90 and 91).

These mechanisms represent the nucleophilic and radical versions. The authors of the cited study[175] believed that the radical pathway is more probable because even small amounts of reducing metals can efficiently initiate the chain process.

Scheme 90

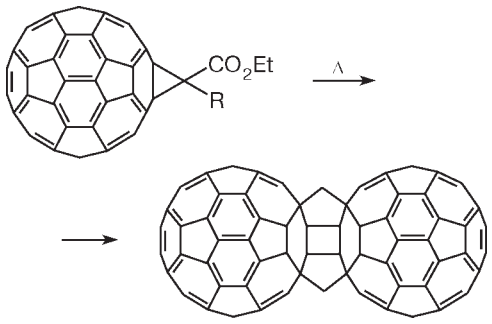


Scheme 91



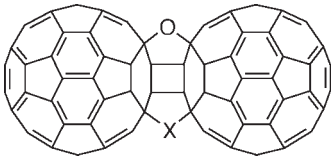
Thermolysis of ethoxycarbonylmethano-1,2-dihydrofullerenes produced the new $C_{122}H_4$ dimer in which two fullerene cages are linked by two C—C bonds and two methylene bridges.[176] The MO calculations demonstrated that the close arrangement of two fullerene cores leads to substantial overlapping of their HOMOs and LUMOs resulting in electronic interaction between the fullerene fragments (stepwise electrochemical reduction of each core at different potentials was found). The mechanism of formation of the dimer remains unclear. However, the authors assumed decomposition of cyclopropane yielding the biradical followed by the formation of the dimer (Scheme 92).

Scheme 92



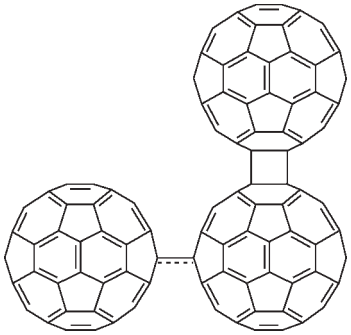
R = H, CO_2Et

Thermolysis of $C_{120}O$ gave rise to the analogous C_{2v}-symmetrical dimer[177] bridged by the oxygen atoms instead of the methylene groups. Thermolysis in the presence of sulfur afforded the dimer containing one oxygen bridge and one sulfur bridge.[178]



X = O, S

Calculations of the total energies of various regioisomeric trimers of C_{60} by the empirical tight-binding method and the semiempirical quantum-chemical PM3, AM1, and MNDO methods demonstrated that the equatorial isomer (C_s) is the most stable one of 10 possible regioisomers.[179]



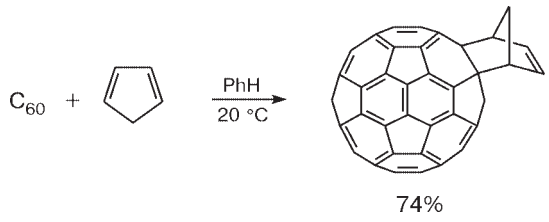
Equatorial (C_s) isomer

4. [2+4]-Cycloaddition

4.1. Preparation of Diels—Alder adducts of fullerene

The dienophilic properties of fullerene in [2+4]-cycloaddition reactions were first revealed in the study of the reaction of fullerene with an excess of cyclopentadiene.[68] However, the authors of the cited study[68] failed to isolate the monoadduct as well as to determine the regiochemistry of the resulting polyadducts. More recently, it was found[180] that the addition of 1.2 equiv. of freshly distilled cyclopentadiene to a solution of fullerene in benzene at 20 °C afforded the Diels—Alder monoadduct in 74% yield (Scheme 93).

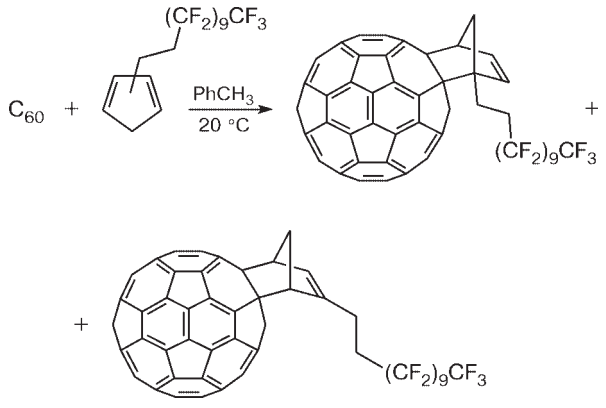
Scheme 93



The monoadduct was also readily derived from pentamethylcyclopentadiene.[181] This cycloaddition product is less susceptible to the retro-Diels—Alder reaction compared to the adduct with cyclopentadiene by itself. The adducts obtained by the reactions of fullerene with cyclopentadienone or its ethylene ketal are even more thermally stable.[182] To prevent reversibility of cycloaddition, the double bond of the resulting cycloadduct can be hydrogenated, with the consequent formation of the thermally stable compound.[183]

Although perfluoroalkylcyclopentadiene is less reactive in cycloaddition to fullerene than unsubstituted cyclopentadiene, the use of this compound allows the preparation of the adduct possessing unusual properties[184] (Scheme 94).

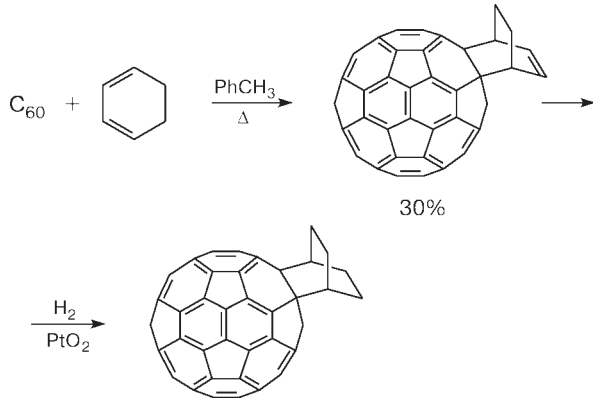
Scheme 94



Interestingly, the reaction products are readily soluble in Freon 113 but are poorly soluble in another "fluorine-rich phase," *viz.*, in perfluorohexane.

As in the reactions with other dienophiles, cyclohexadiene exhibits somewhat lower reactivity than cyclopentadiene to give (under similar conditions) the cycloadduct in a yield of only 30%. Hydrogenation of the adduct afforded the compound resistant to fragmentation according to the retro-Diels—Alder reaction[185] (Scheme 95).

Scheme 95

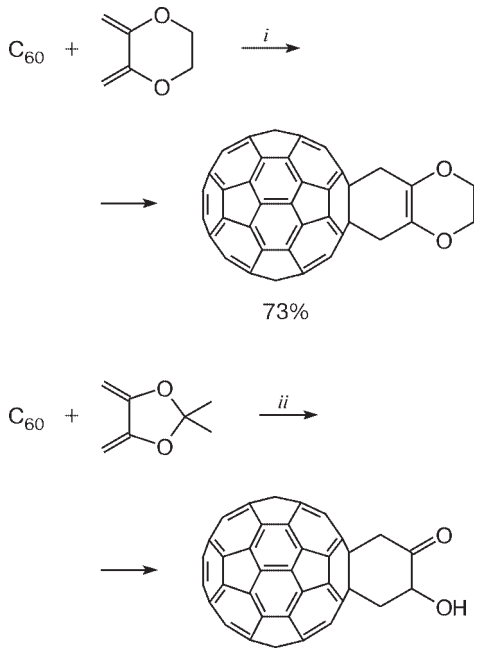


The lower reactivity of cyclohexa-1,3-diene as compared to cyclopentadiene is generally attributed to the larger distance between the C(1) and C(4) atoms (r_{1-4}) in cyclohexadiene compared to cyclopentadiene.[186] An analogous explanation was provided[187] for the difference in the reactivity of three 2,3-dioxy-substituted butadienes in the reactions with C_{60}. 2,3-Dimethylene-1,4-dioxane (r_{1-4} = 3.226 Å) exhibits much higher reactivity than 4,5-dimethylene-2,2-dimethyl-1,3-dioxolane (r_{1-4} = 3.385 Å). Thus, the former compound readily added to fullerene even at room temperature, whereas the latter compound was inactive even at 80 °C and was involved in cycloaddition only under high pressure (Scheme 96).

Due to the electron-deficient properties, fullerene serves as a rather reactive dienophile. Actually, the reactivity of fullerene as a dienophile is comparable with those of maleimides.[188] In some cases, fullerene is even substantially more reactive than typical dienophiles.[189,190] As would be expected for normal electron demand [2+4]-cycloaddition,[191] fullerene is readily involved in reactions with dienes containing electron-donating substituents. Thus, refluxing of fullerene with 2 equiv. of 1-trimethylsilyloxybutadiene followed by hydrolysis afforded 1-hydroxy-1,4-dihydrobenzo[*b*]fullerene in 66% yield[115,192] (Scheme 97).

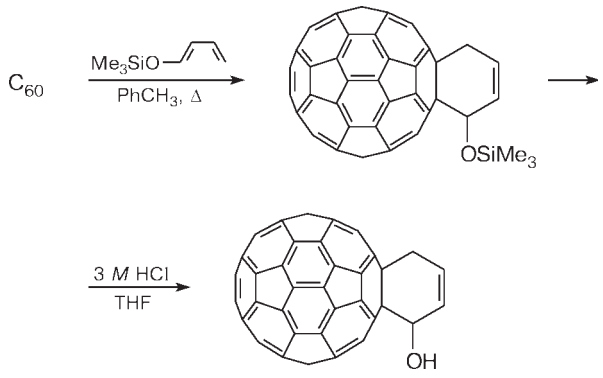
2-Trimethylsilyloxybutadiene,[193,194] 3-trimethylsilyloxypenta-1,3-diene, 1-methoxy-3-trimethylsilyloxybutadiene,[188] 2-trimethylsilyloxycyclohexa-1,3-diene, and

Scheme 96



Reagents and conditions: *i*. PhMe, 25 °C, 12 h; *ii*. 1) 300 MPa, 24 h, 2) TFA.

Scheme 97

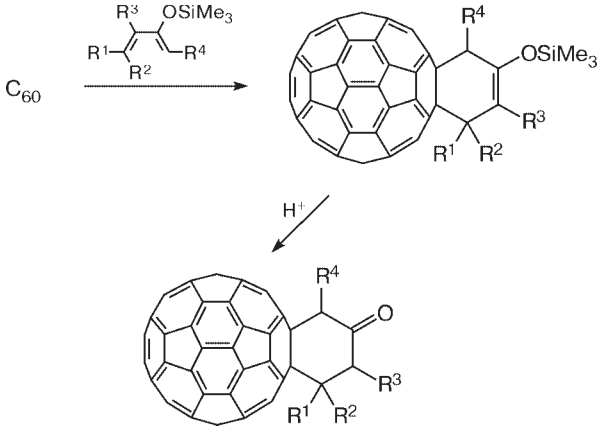


other substituted silyloxydienes reacted analogously.[195] Hydrolysis of the adducts gave rise to the corresponding stable ketones (Scheme 98).

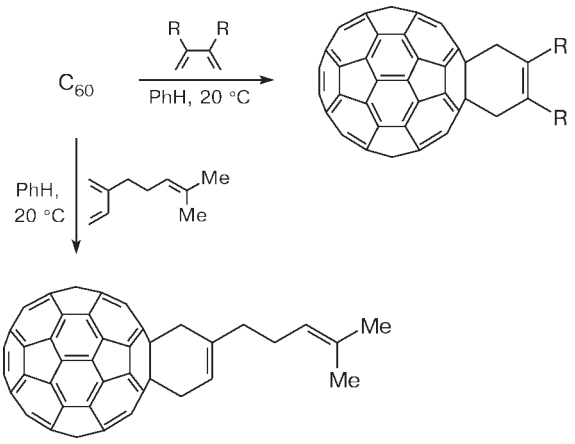
The reactions of fullerene with 2,3-dipropylbutadiene,[185] 2,3-dimethylbutadiene, myrcene,[196] activated furans,[197] and other dienes[198—202] were also studied (Scheme 99).

The use of chiral dienes makes allows the synthesis of optically active fullerene derivatives. Thus, the reaction of fullerene with (*R*)-nopadiene proceeded selectively to give the only adduct in 64% yield[163] (Scheme 100).

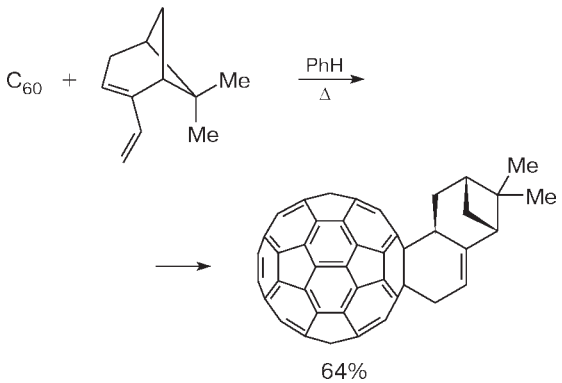
Scheme 98



Scheme 99

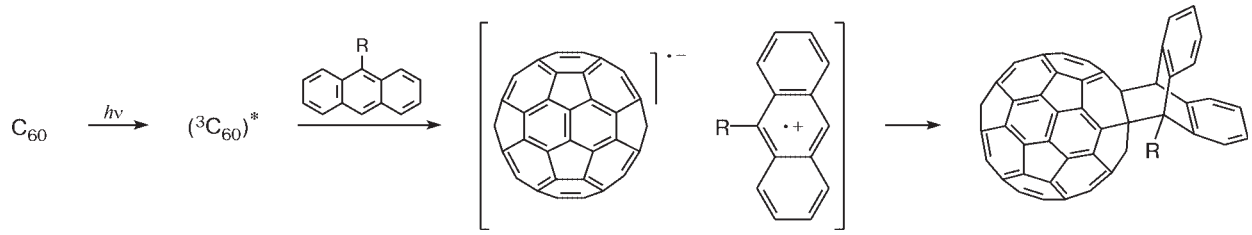


Scheme 100



Anthracene derivatives are extensively used as reactive dienes in Diels—Alder reactions. It is not surprising that anthracene derivatives were among the first dienes in-

Scheme 101



volved in cycloaddition to fullerene.[203–209] Later on, it was found that the reaction with anthracene is accelerated under irradiation of the reaction mixture. At room temperature, fullerene does not react with anthracene without irradiation. However, irradiation of a solution of equimolar amounts of fullerene C_{60} and anthracene in benzene for 9 h afforded mono- and bis-adducts in yields (NMR control) of 10 and 26%, respectively, along with the anthracene dimer.[210] Under these conditions, anthracene is not involved in cycloaddition to fullerene in the absence of the solvent. To the contrary, 9-methylanthracene produced a mixture of mono- and bis-adducts (30 and 19%, respectively) without the formation of the self-condensation product.[210] This difference was accounted for by the stepwise mechanism with the photoinduced electron transfer in the first step (Scheme 101).

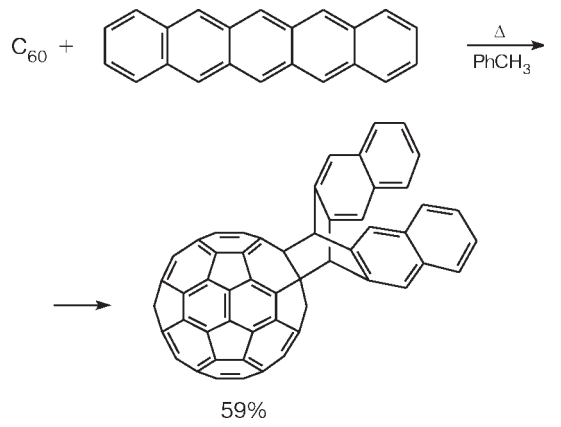
In the case of anthracene, this step is endothermic and the high energy barrier is to be overcome. The insertion of the methyl group leads to a decrease in the ionization potential of anthracene resulting in a decrease in the energy of the transition state. This explanations is consistent also with the fact that the reactions do not take place in solvents, which are usually used in this type of cycloaddition (benzene and its derivatives). When the reactions are carried out in solutions, the energy of solvent reorganization makes a substantial contribution to the thermodynamic barrier, whereas stabilization of the resulting radical-ion pair by low-polarity solvents is too small to compensate this undesirable effect.

The results of investigation of the kinetic isotope effects led to the conclusion that the thermally induced Diels—Alder reactions of C_{60} with both anthracene and its 9,10-dimethyl derivative (DMA) proceeded according to the concerted mechanism.[211] In the case of the stepwise mechanism through the formation of the dipolar or biradical intermediate, one would expect the normal secondary kinetic isotope effect upon the replacement of the α-hydrogen atom and the substantial β-secondary kinetic isotope effect. The determined k_H/k_D values of 0.93 (0.96 per deuterium atom) and ~1.0 are inconsistent with the stepwise mechanism. In the reaction of fullerene with 2,3-dimethylene-7-oxanorbornane, the much more substantial reverse α-kinetic isotope effect (k_H/k_{4D} = 0.61, k_H/k_D = 0.88 per deuterium atom) was observed.[212] The symmetrical structure of the transition state was confirmed by the fact that the kinetic isotope effect (per deuterium atom) for the 2,3-bis(dideuteriomethylene) derivative is equal to that for the 2-(dideuteriomethylene)-3-methylene derivative. The smaller reverse isotope effect in the case of cycloaddition of anthracenes is attributable to the "earlier" transition state in the reactions involving these compounds. The concerted reaction mechanism of [2+4]-cycloaddition was also confirmed by the results of both semiempirical and *ab initio* quantum-chemical calculations for the Diels—Alder reactions of fullerene.[213–217]

Essential acceleration of [2+4]-cycloaddition was also observed upon microwave irradiation of the reaction mixture. The C_{60} adduct with anthracene was obtained in 35% yield after irradiation of a toluene solution for 15 min,[218] whereas heating in benzene for 12 h afforded the cycloadduct in 25% yield.[205] In refluxing toluene, the yield of the Diels—Alder adduct was only 12%.[203] The addition product was obtained in somewhat higher yield (39%) only after heating of the reagents in a naphthalene solution for 48 h.[204]

The efficiency of the cycloaddition of anthracenes and their analogs can be improved by performing the reactions under the conditions of high-speed vibration grinding of solid reagents (the mechanochemical synthesis).[219] In the reaction with anthracene (1.2 equiv.), the Diels—Alder monoadduct was obtained in 55% yield after the above-described treatment for 1 h. The reaction afforded also a mixture of isomeric bis-adducts as byproducts in 19% total yield. Mechanochemical cycloaddition of tetracene and naphtho[2,3-*a*]pyrene produced also the Diels—Alder adducts in high yields (61% and 51%, respectively). Both the low temperature and the absence of the solvent are of importance. It was demonstrated that the solution-phase cycloaddition of 9,10-dimethylanthracene to fullerene at room temperature proceeded reversibly.[206] To the contrary, fast separation of the mixture that formed after mechanochemical treatment of these reagents (30 min) made it possible to isolate the Diels—Alder monoadduct in 62% yield.[219] When dissolved, this cycloadduct was subjected to ready dissociation to give fullerene and 9,10-dimethylanthracene with the half-life of about 2 h. Simple grinding of a mixture of

Scheme 102



fullerene and anthracene in a mortar is inefficient (according to the chromatographic data, the yield of the adduct was only 2.3%) because the energy barrier to cycloaddition is too high for the reaction to proceed under weak mechanical treatment.

In principle, higher linear acenes can form both various regioisomers of the monoadduct and bis-adducts. It was found[220] that refluxing of equimolar amounts of pentacene and C_{60} fullerene in a toluene solution afforded a cycloaddition product at the central C(6) and C(13) atoms in 59% yield (Scheme 102). The use of a tenfold excess of fullerene made it possible to increase the yield to 86% (with respect to the consumed pentacene).

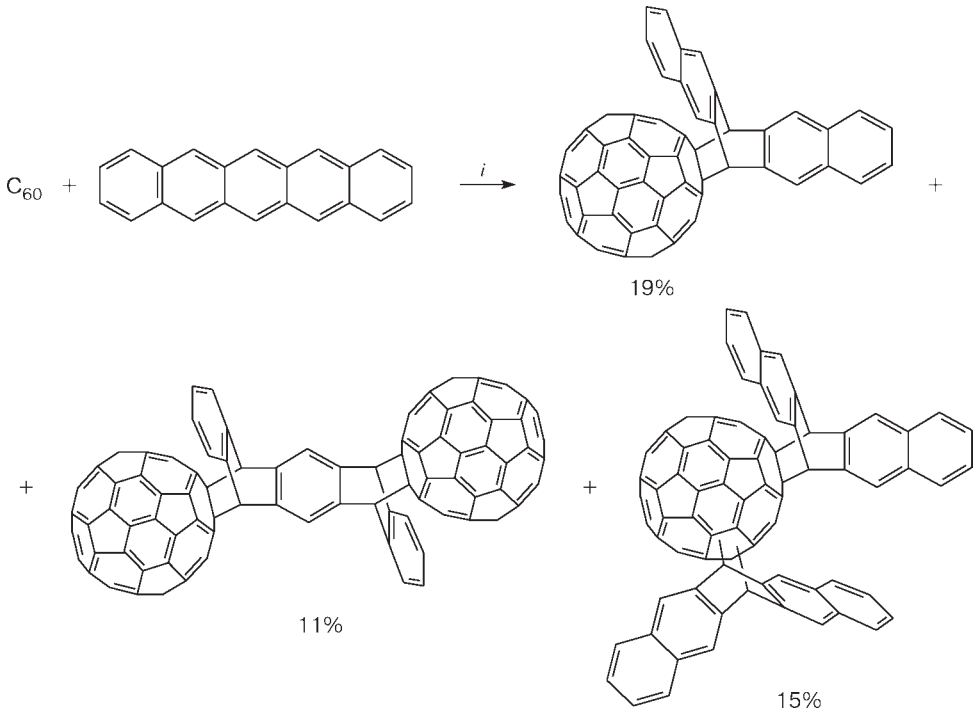
Under the conditions of the solid-phase mechanochemical synthesis, the reaction of equimolar amounts of the same reagents afforded a mixture of addition products (1:1, 1:2, and 2:1). The monoadduct was obtained as the major reaction product (19%). In addition, the *trans*-bisfullerene adduct and isomeric bis(pentaceno)fullerenes were isolated in 11% and 15% yields, respectively[219] (Scheme 103).

The use of two equivalents of fullerene made it possible to increase the yield of bis(fullereno)pentacene up to 16%.

Interestingly, the insertion of aryl substituents at positions 6 and 13 of pentacene leads to reversal in selectivity of cycloaddition. In this case, the *cis*-bisfullerene adducts were obtained in good yields (85% for R = Ph; 75% for R = 4-hydroxyphenyl; 5 equiv. of fullerene)[221] (Scheme 104).

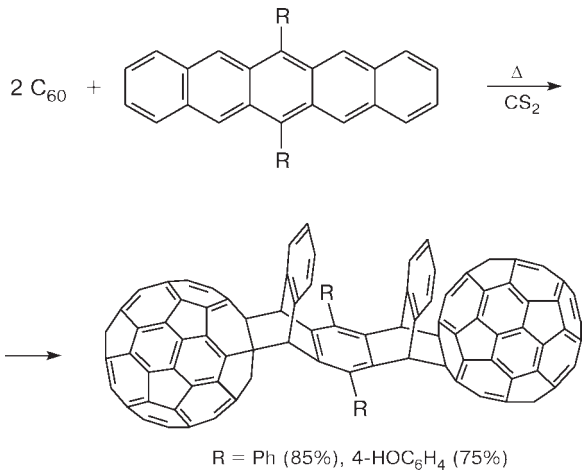
To account for the difference in the behavior of ubsubstituted and 6,13-diaryl-substituted pentacenes, semiempirical quantum-chemical PM3 calculations were carried out using bicyclopentylidene as a model of fullerene. The results of these calculations demonstrated that in the case of formation of the monoadduct, the addition at the central nucleus (C(6)—C(13)) is more favorable from the standpoint of both thermodynamics (the enthalpy of formation is 4.0 kcal mol^{-1} lower) and kinetics

Scheme 103



i. A mill.

Scheme 104



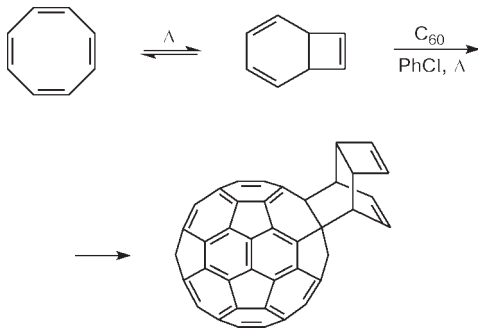
R = Ph (85%), 4-HOC_6H_4 (75%)

(the activation barrier is 1.4 kcal mol^{-1} lower) as compared to the addition at the C(5)—C(14) atoms. The insertion of aryl substituents at positions 6 and 13 leads to reversal in stability of the cycloadducts and, as a consequence, to reversal in reactivity, this difference being increased as the size of the dienophile increases.[221] Under both the kinetic and thermodynamic control, the *syn*-bis-adducts dominate over the *trans*-isomers.[222] The fact is attributable to specific interactions between the fullerene cages. Thus, cycloaddition of dimethyl acetylenedicarboxylate gave rise to both the *syn*- and *anti*-bis-adducts in a ratio of 1 : 1.3.[222] To test this assumption, the authors performed cycloaddition of fullerene to 6,13-bis(trimethylsilylethynyl)pentacene whose bulky substituents hinder stabilizing π-folding interaction between the fullerene cores in the transition state in the second step of cycloaddition. In this case, the monoadduct was actually isolated in 75% yield upon refluxing of the reagents in carbon disulfide for 24 h. The bis-adducts were formed more slowly, both the *cis*- and *trans*-bis-adducts being present in the reaction mixture. However, the authors failed to unambiguously establish the major stereoisomer (the ratio of two isomers was approximately 2.5 : 1).[222]

The adducts of C_{60} with anthracene and its derivatives are quite stable at room temperature but they decompose upon heating.[205,206] The reversibility of this reaction was studied in more detail[223] by ^{3}He NMR spectroscopy using the $^3He@C_{60}$ inclusion compound. It was found that the reaction of C_{60} with a large excess (15 equiv.) of DMA produced mono-, bis-, tris-, and tetrakis-adducts. The equilibrium constant of the formation of the monoadduct decreases from 3600 at 295.4 K to 100 at 325.0 K. At 295 K, the K_2, K_3, and K_4 constants are 490, 41, and 2.3 L mol^{-1} for the bis-, tris-, and tetrakis-adducts, respectively. The values of ΔG, ΔH, and ΔS, which were determined from the temperature dependence of K_1 and K_2 in the range from 295.4 to 325.0 K, are −4.8 kcal mol^{-1}, −22.9 kcal mol^{-1}, and −61.2 cal $(mol\ K)^{-1}$, respectively, for the formation of the monoadduct and −3.7 kcal mol^{-1}, −22.5 kcal mol^{-1}, and −63.7 cal $(mol\ K)^{-1}$, respectively, for the transformation of the monoadduct into the bis-adduct. These values can be used for the estimation of the temperatures at which the equilibrium constants are equal to unity, *i.e.*, the rates of the Diels—Alder reactions are equal to the rates of the reverse processes. For the formation of the monoadduct and its transformation into the bis-adduct, these temperature are 374 and 353 K, respectively. Analogous measurements were carried out for cycloaddition of fullerene C_{70}. In the latter case, the equilibrium constants for the formation of the mono- and bis-adducts were demonstrated to be smaller (by a factor of 4—7) due primarily to the less negative thermal effect of the formation of the adduct (−21.1 kcal mol^{-1} for the monoadduct).[223] The kinetic and synthetic aspects of the reversibility of [2+4]-cycloaddition were also considered in other studies.[224—226]

It is known that cyclooctatetraene is involved in many [2+4]-cycloaddition reactions after electrocyclic isomerization into bicyclo[4.2.0]octa-2,4,7-triene. It is not surprising that refluxing of fullerene C_{60} in chlorobenzene with 5 equiv. of cyclooctatetraene afforded the corresponding cycloadduct[227] in 79% yield (48 h) (Scheme 105).

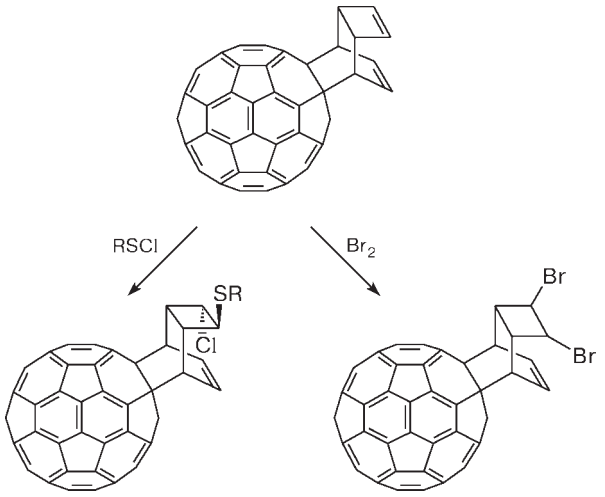
Scheme 105



[2+4]-Cycloaddition of cyclooctatetraene also proceeded reversibly, as follows from a decrease in the yield of the adduct with increasing temperature. Prolonged heating at 180 °C gave rise to only trace amounts of the cycloadduct. At the same time, this adduct is quite stable at room temperature and can be stored for 3 months without decomposition. This stability makes it possible to carry out its functionalization to form products of electrophilic addition or epoxydation of the double bond of the cyclobutene moiety in the adduct[227] (Scheme 106).

It should be noted that the direction of electrophilic addition to this adduct differs noticeably from that ob-

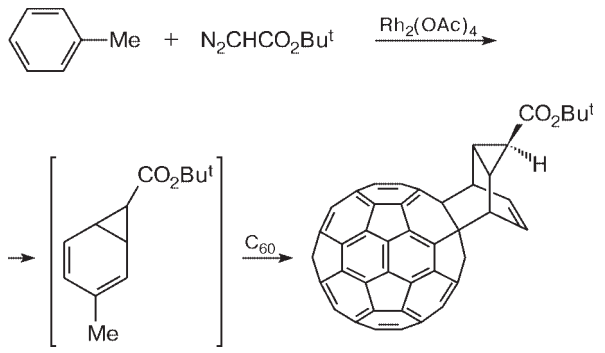
Scheme 106



served for the adducts of cyclooctatetraene with traditional dienophiles which produced primarily products of cross- and *cis*-addition of electrophilic reagents.[228]

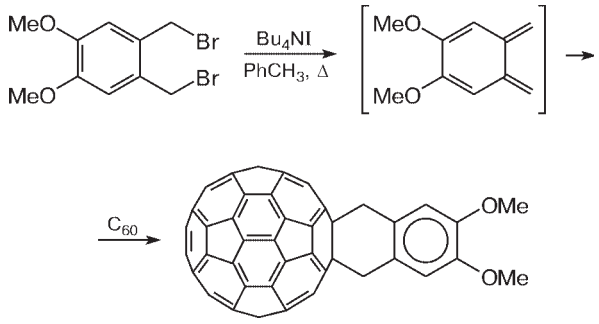
Unlike cyclooctatetraene, cycloheptatriene reacted with fullerene in both isomeric forms, *viz.*, as cycloheptatriene and norcaradiene,[229,230] the adduct derived from norcaradiene being a kinetically controlled product.[229] An alternative procedure for the preparation of the [2+4]-cycloaddition adduct of fullerene with norcaradienes was also reported.[231] In the latter case, $Rh_2(OAc)_4$ was added to a solution of fullerene and *tert*-butyl diazoacetate (1 : 3) in toluene. The resulting carbenoid reacted with thermodynamically more stable toluene to generate the norcaradiene derivative. Its Diels—Alder reaction with fullerene gave the cycloadduct in 43% yield (Scheme 107). In this reaction, methanofullerene was obtained as a by-product in only 4% yield.

Scheme 107



The analogous reaction in a benzene solution afforded the Diels—Alder adduct in 24% yield. The *anti-exo* orientation of cycloaddition is accounted for by essential steric

Scheme 108

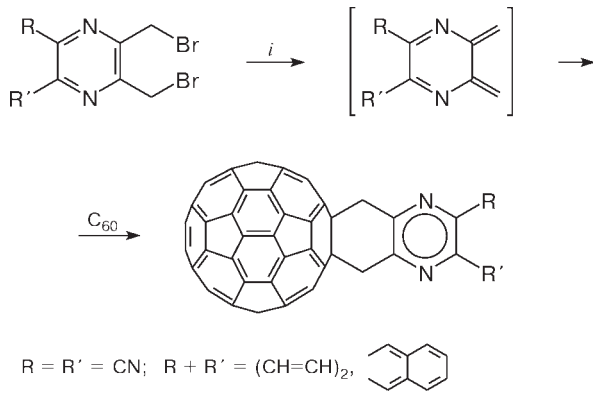


requirements of the *tert*-butoxycarbonyl group. The resulting cycloadduct can further be transformed into the corresponding acid and its derivatives.

Cycloaddition becomes irreversible in the case that the resulting double bond of the cycloadduct is involved in the aromatic system as, for example, in the reaction with isobenzofuran.[232] However, most of such dienes derived from *o*-quinodimethane are unstable because they undergo fast aromatization. The *in situ* generation of *o*-quinodimethane derivatives provides the basis for the preparation of highly reactive dienes, which are involved in irreversible [2+4]-cycloaddition to C_{60}.[233—249] Several methods for generation of *o*-quinodimethanes are available. Iodide-induced 1,4-dehalogenation of *o*-bis(bromomethyl)benzenes is most commonly used for this purpose. This method was used for the preparation of a variety of Diels—Alder adducts of [60]fullerene.[250—254] As an example we refer to heating of 1,2-bis(bromomethyl)-4,5-dimethoxybenzene with tetrabutylammonium iodide in toluene[255] (Scheme 108).

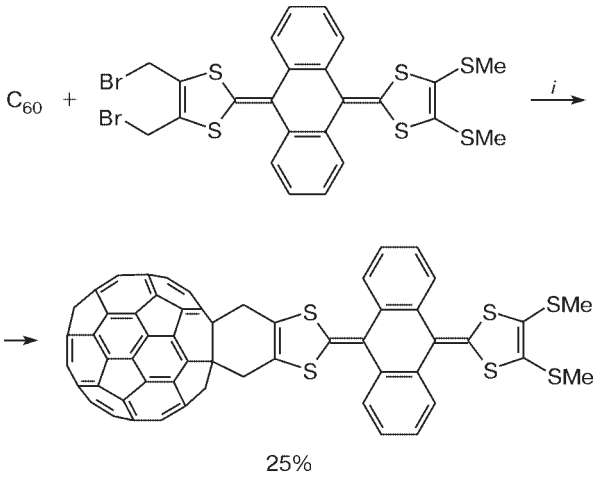
Analogous procedures were used for the synthesis of fullerene adducts with 1,4-dimethoxy- and 1,4-dihydroxy-2,3-bis(bromomethyl)anthraquinone[256] as well as of vari-

Scheme 109



i. NaI, 18-crown-6, $1,2\text{-}Cl_2C_6H_4$, Δ.

Scheme 110



i. NaI, 18-crown-6.

ous fullerenothiophenes[236,257] and fullerenoquinoxalines[258,259] (Scheme 109).

It should be noted that the reaction rate and the yield of the product were substantially increased under ultrasonic irradiation (in the case of 2,3-bis(bromomethyl)quinoxaline, the Diels—Alder adduct was obtained in 22% and 37% yields upon refluxing in *o*-dichlorobenzene for 24 h and under ultrasonic irradiation for 30 min, respectively).

The reaction of fullerene with *o*-quinodimethane generated from the corresponding *o*-bis(bromomethyl)arenes produced also photoactive compounds containing both the electron-withdrawing fullerene moiety and the electron-donating tetrathiafulvalene fragment or its analogs[260—262] (Scheme 110).

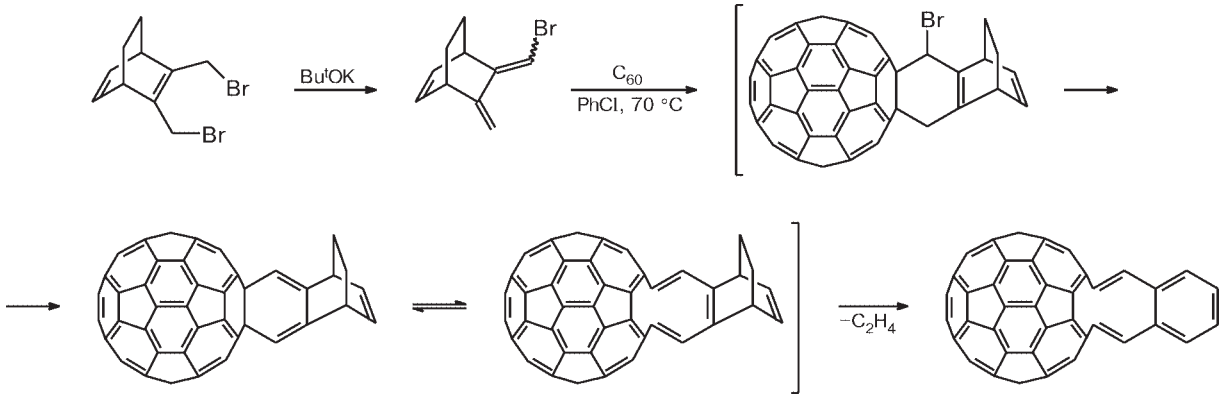
Unlike the action of the NaI—18-crown-6 system, treatment of 2,3-bis(bromomethyl)[2.2.2]octa-2,5-diene with potassium *tert*-butoxide gave bromodiene through dehydrohalogenation. The resulting adduct of this diene with fullerene is unstable and eliminates HBr under the reaction conditions to produce the fullerenocyclohexadiene derivative. However, the latter compound is too unstable to be isolated and decomposes to form unusual fulleroid[263] (Scheme 111).

Another procedure for generation of *o*-quinodimethane derivatives involves photochemical isomerization of *o*-toluyl aldehyde and its analogs[264] (Scheme 112).

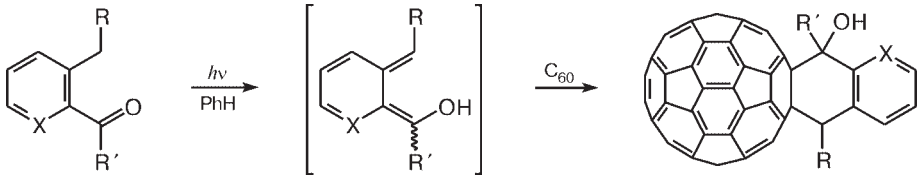
These reactions afforded cycloadducts in 68—88% yields. However, this approach seems to be of very limited application. Thus it was found that irradiation of *o*-methylbenzophenone in the presence of C_{60} initially produced the unstable cycloadduct, which decomposed to give 1-(2-benzoylphenyl)methyl-1,2-dihydrofullerene[265] (Scheme 113).

Since generation of the diene by the thermally induced rearrangement of 3-phenylbenzocyclobutenol afforded also the hydroalkylation product rather than the [2+4]-cycloaddition adduct, it can be concluded that the

Scheme 111

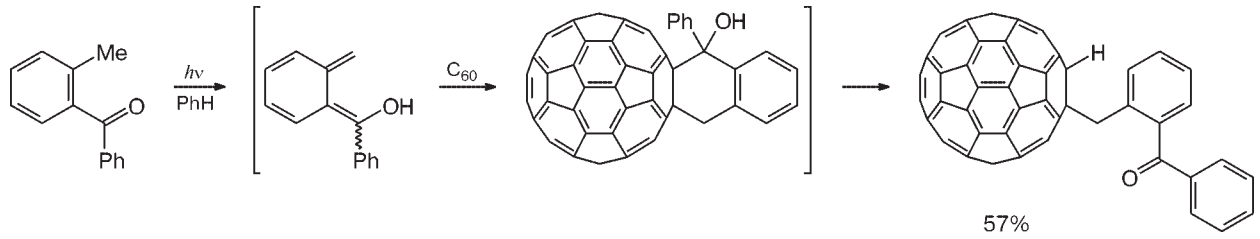


Scheme 112

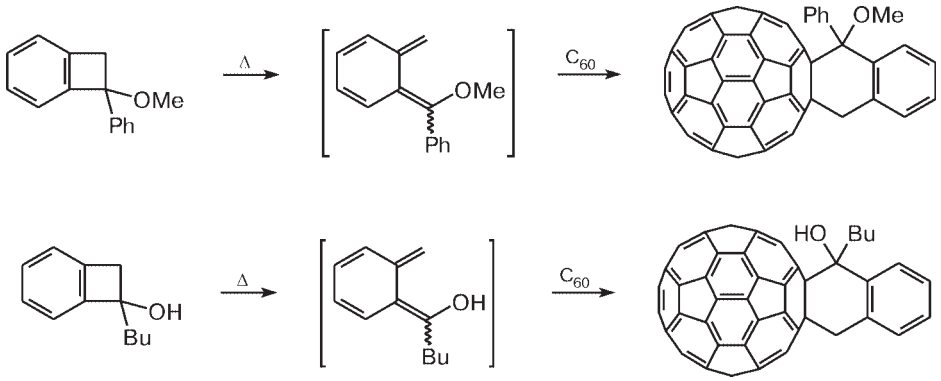


X = CH, R = R′ = H (86%); R = Me, R′ = H (85%);
R = H, R′ = Me (68%); X = N, R = R′ = H (88%)

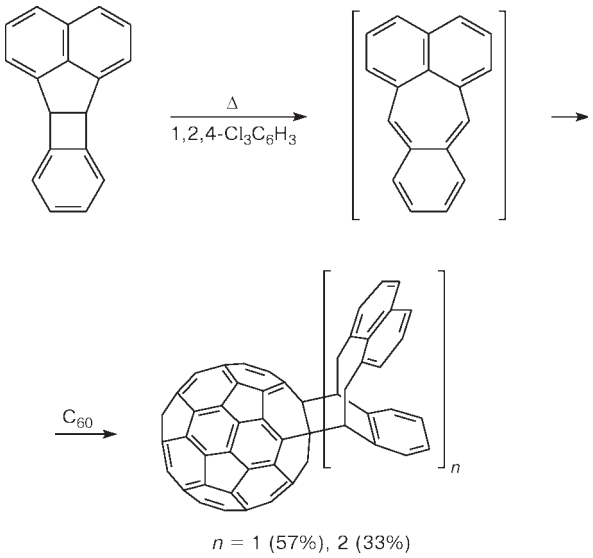
Scheme 113



Scheme 114



Scheme 115



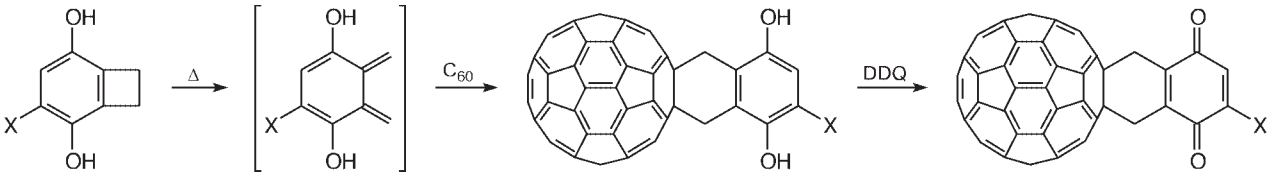
above-considered transformation is associated with instability of the resulting Diels—Alder adduct due to proton transfer from the hydroxy group. To the contrary, heating of 3-methoxy-3-phenylbenzocyclobutene with fullerene yielded the cycloaddition product, which was stable upon prolonged refluxing in toluene. Thermolysis of 1-butyl-1-hydroxybenzocyclobutene in the presence C_{60} also yielded a stable adduct (Scheme 114).

Thermolysis of benzocyclobutenes provides the general procedure for generation of *o*-quinodimethanes, including the preparation of very unusual cycloadducts[266] (Scheme 115).

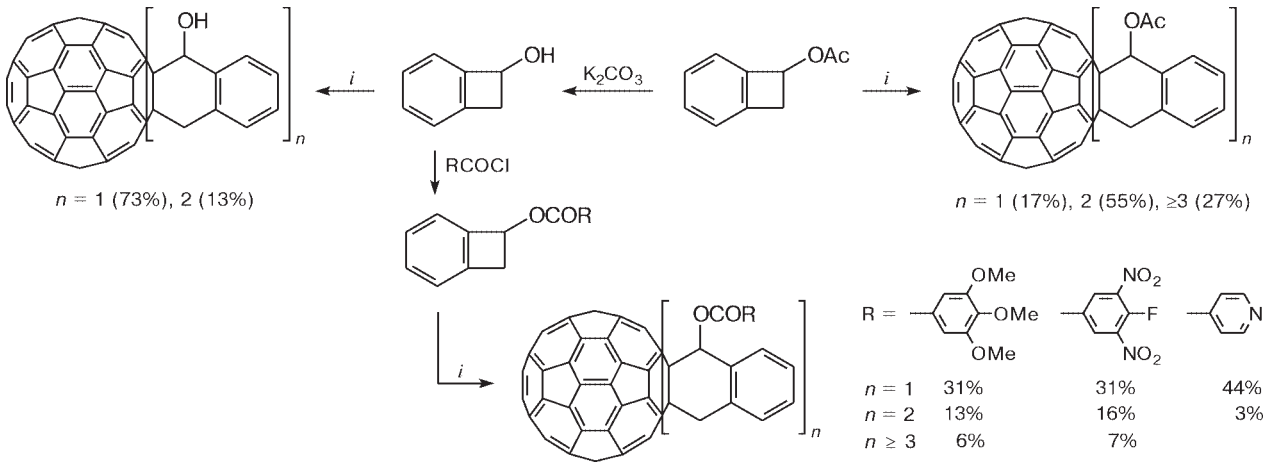
Heating of fullerene with 3,6-dihydroxybenzocyclobutenes followed by oxidation of the resulting adduct with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produced fullerenobenzoquinones (X = H[267] or Cl [268]) (Scheme 116).

This procedure is particularly suitable for the synthesis of fullerenodecalins containing various substituents at the benzyl carbon atom. For example, this approach was ap-

Scheme 116



Scheme 117

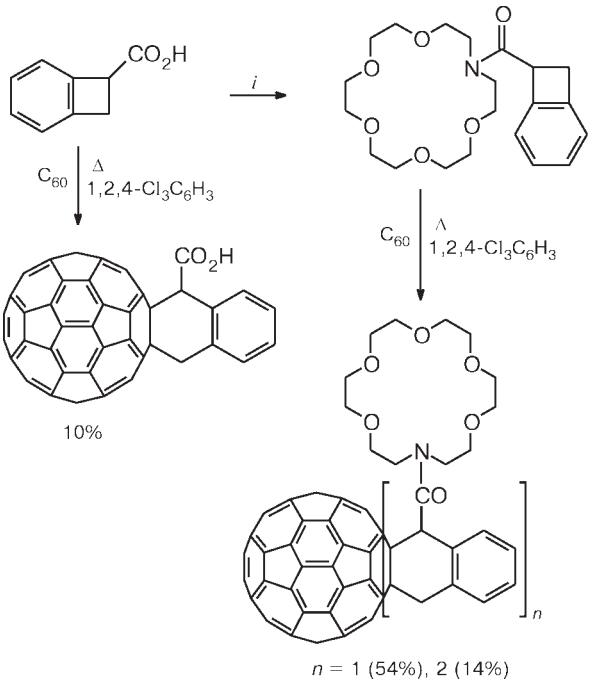


i. C_{60}, 1,2,4-$Cl_3C_6H_3$, Δ.

plied to the synthesis of hydroxy-[237] and acyloxy-substituted[266] derivatives (Scheme 117).

Benzocyclobutenes bearing a carboxy substituent react analogously (Scheme 118).

Scheme 118

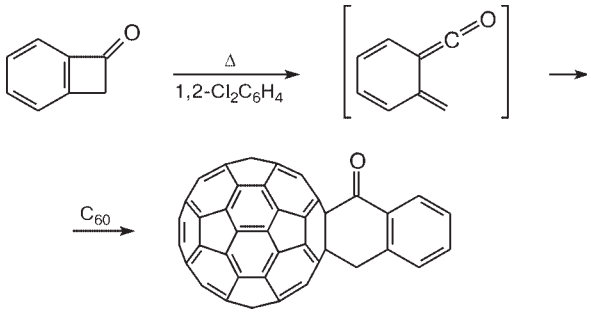


i. aza-18-crown-6, DCC.

Heating of benzocyclobutenone in *o*-dichlorobenzene in the presence of fullerene afforded fullerenodecalone through a similar mechanism[269] (Scheme 119).

This method was also employed for the preparation of fullerene-containing high-molecular-weight compounds

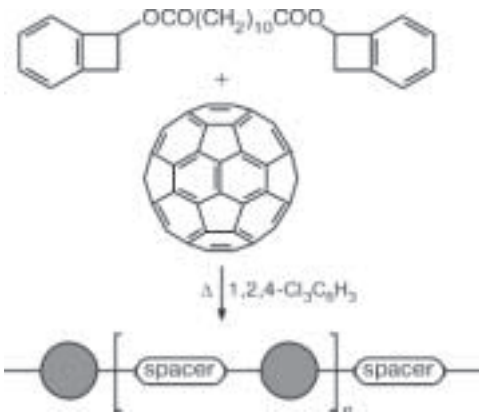
Scheme 119



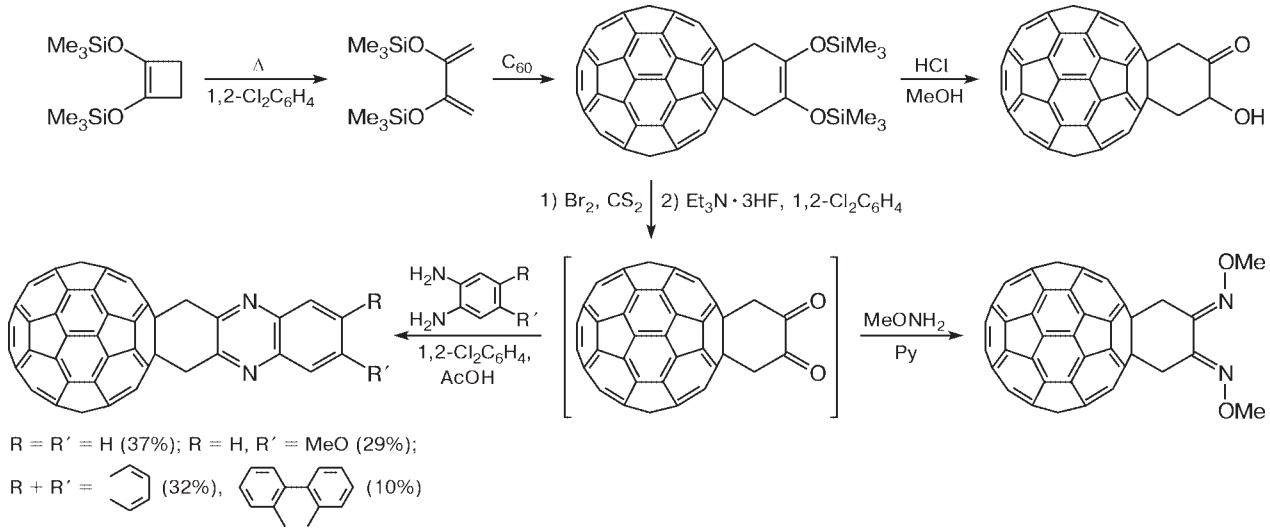
with the use of the bis(benzocyclobutene) derivative as a source of diene[269] (Scheme 120).

Heating of 1,2-bis(trimethylsilyloxy)cyclobutene with 0.6 equiv. of fullerene in 1,2-dichlorobenzene gave rise to the monoadduct whose hydrolysis produced the above-described acyloin in a total yield of 89%. The low-temperature treatment of the initial cycloadduct with bro-

Scheme 120



Scheme 121

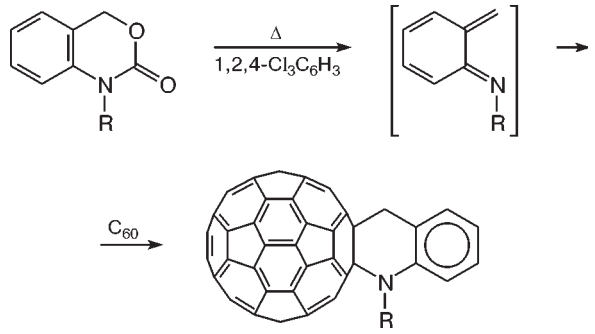


mine yielded unstable diketone, which can be either isolated as bis(*O*-methyl)oxime or transformed *in situ* into phenazine derivatives[270] (Scheme 121).

Unlike the reactions of most of other benzocyclobutenes, the cycloadduct of fullerene with 1,1,2,2-tetraisopropylbenzo-1,2-disilacyclobutene was isolated only upon irradiation of the reaction mixture in the presence of *tert*-butyl alcohol. In the absence of the alcohol, fullerene was completely consumed, but a unidentified mixture was obtained.[62]

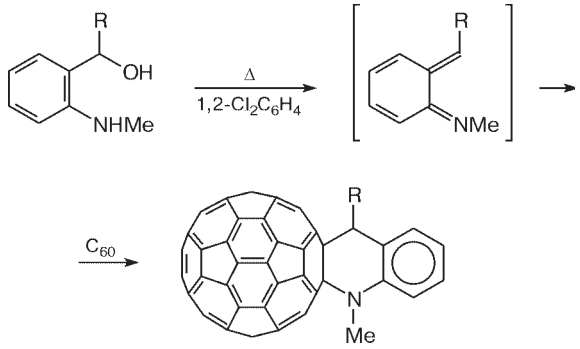
Heterocyclic fullerene derivatives can also be prepared by the Diels—Alder reaction of fullerene with heterodiene. The latter are commonly generated *in situ*. For example, 1-aza-substituted dienes were prepared by decarboxylation of 3,1-benzoxazin-2-one derivatives[271] (Scheme 122).

Scheme 122



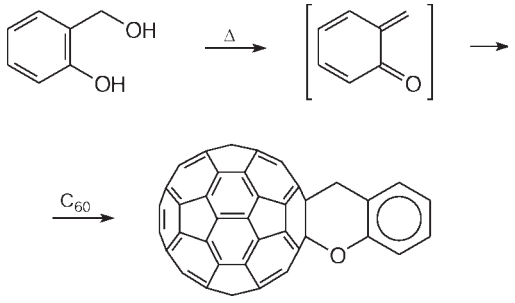
Thermolysis of *o*-aminobenzyl alcohols also afforded reactive *o*-quinonemethideimines, which reacted with fullerene to give fullerenoquinolines[272] (Scheme 123).

Scheme 123



Analogously, *o*-quinonemethide, which was used for the synthesis of fullerenochromans, was generated by thermolysis of *o*-hydroxybenzyl alcohol[273] (Scheme 124).

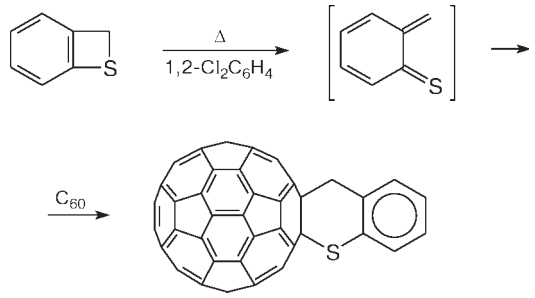
Scheme 124



As in the case of anthracene, the reaction was accelerated under microwave irradiation.[218]

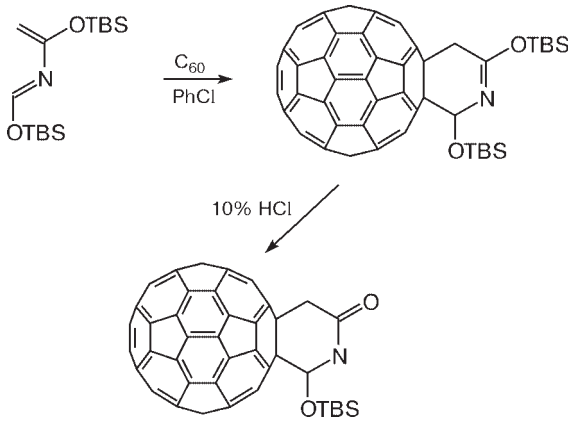
To the contrary, fullerenothiochroman was prepared by heating of benzothietane, which is a thio analog of benzocyclobutene[274] (Scheme 125).

Scheme 125

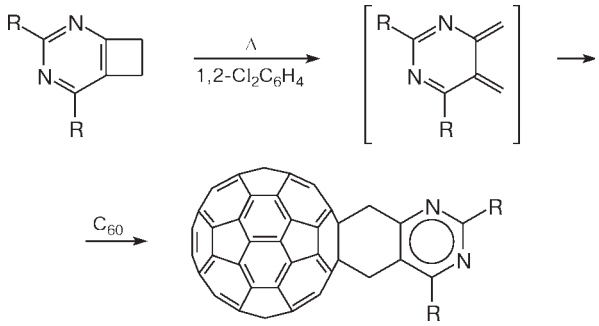


α,β-Unsaturated thiocarbonyl compounds, which can be generated *in situ* by acylation of thioacrylamide, was also used as the diene fragment.[275] Unlike most of other heterodienes, stable 2-azadienes are sufficiently reactive

Scheme 126



Scheme 127

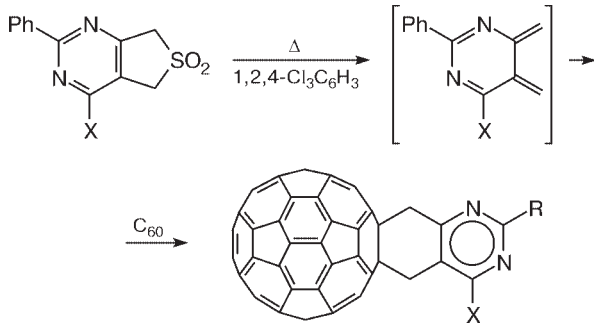


R = Me, Ph, Tol, 4-ClC_6H_4

that they give Diels—Alder adducts with fullerene without significant retro-cleavage under the reaction conditions.[276] However, in this case it is also recommended that the adducts be transformed into the more stable amide form (Scheme 126).

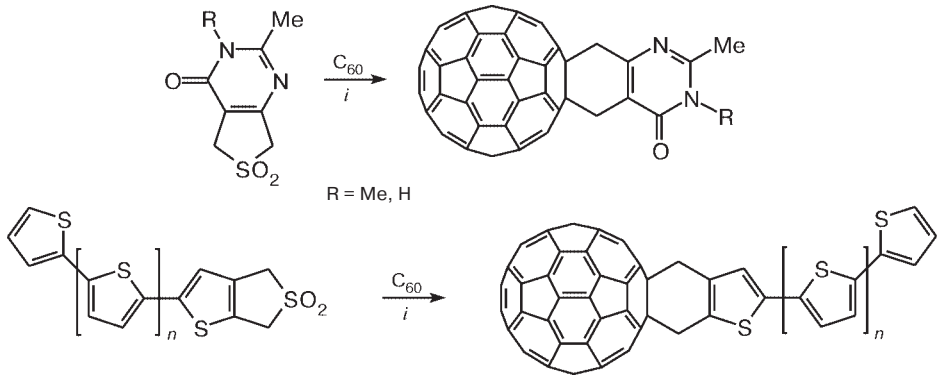
It should be noted that polyadducts were not detected among the products of this reaction even with a threefold excess of the diene.

Scheme 128



X = OMe, piperazin-1-yl

Scheme 129



i. 1,2,3-$Cl_3C_6H_3$, Δ.

Upon heating in *o*-dichlorobenzene, cyclobutapyrimidines were isomerized into the corresponding quinodimethanes whose reactions with C_{60} gave rise to fullerenoquinazolines[277,278] (Scheme 127).

An alternative procedure for generation of the *o*-quinodimethane derivative of pyrimidine consists in heating of the corresponding sulfolene. This procedure was also employed for generation of fullerenoquinazolines[279] (Scheme 128).

Sulfolene derivatives of pyrimidinone, oligothiophenes containing up to five thiophene rings,[257] and other sulfur-containing cyclic compounds[262,280] reacted analogously (Scheme 129).

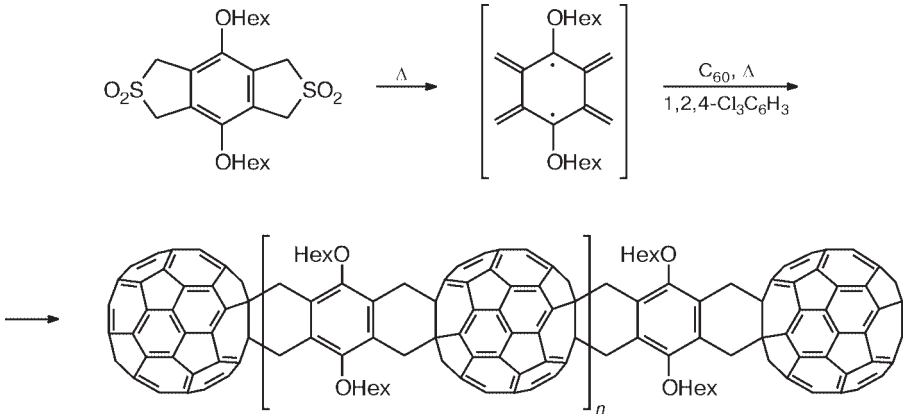
Thermolysis of sulfolenes was used also for generation of oligomeric fullerene derivatives (n = 0—5). The compounds with n = 0 and 1 were isolated by preparative chromatography, and higher oligomers were characterized by mass spectrometry[281] (Scheme 130).

Heating of fullerene with a mixture of disulfone and sulfone sulfoxide afforded another type of oligomers bearing an additional tetrahydronaphthalene fragment in the fullerene core (Scheme 131).

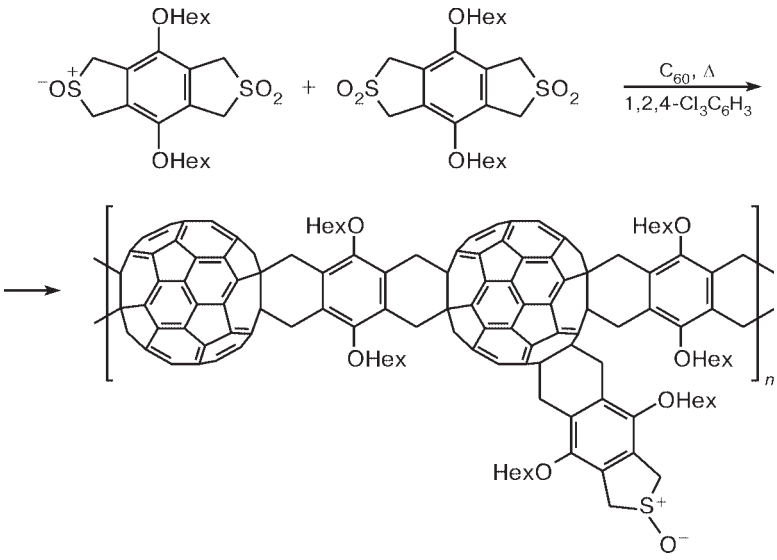
Refluxing of the tetrasulfolene derivative of zinc *meso*-tetraarylporphyrinate with 10 equiv. of [60]fullerene in 1,2-dichlorobenzene for 10—15 h produced porphyrin containing four fullerene substituents[282] (Scheme 132).

Depending on the conditions and duration of the reaction, mono-, bis-, or tris(fullereno)porphyrinates can be obtained as the major products.[282,283] Analogously, the reaction of monosulfolenoporphyrinate with fullerene gave rise to fullerenochlorine characterized by the minimum

Scheme 130

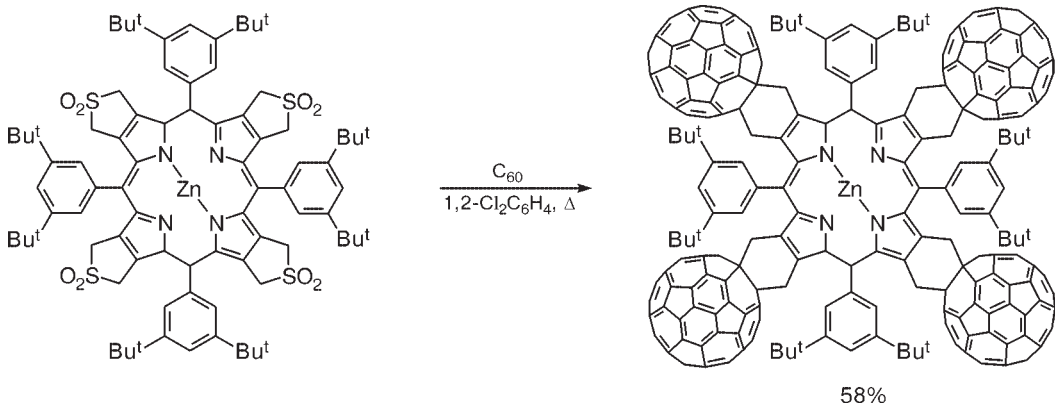


Scheme 131

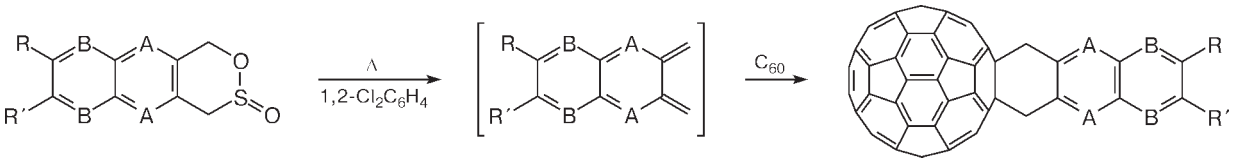


Hex = *n*-C_6H_{13}

Scheme 132



Scheme 133



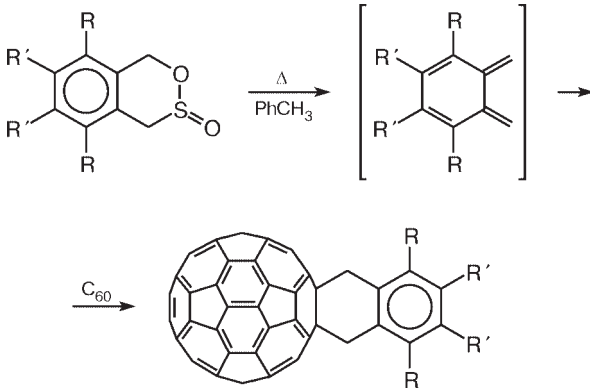
A = N, B = C		A = C, B = N	
R = R′ = H	66%	R = R′ = H	84%
R = R′ = Me	75%	R = R′ = Cl	10%
R = R′ = Cl	53%	R = R′ = Ph	29%
R = Me, R′ = H	51%		

separation between the electron-donating and -withdrawing moieties.[284]

Dienes are formed upon elimination of sulfur dioxide not only from sulfolene derivatives but also from sultines[285,286] (Scheme133).

It was demonstrated that the reaction proceeded more rapidly and efficiently under ultrasonic irradiation[287] (Scheme 134).

Scheme 134

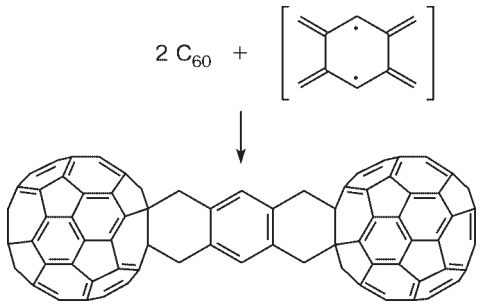


R	H	OC_6H_{13}	OMe	OMe	OMe
R′ (R′—R′)	H	H	H	Br	—(CH=CH)$_2$—
Yield (%)	47	55	47	32	22

Then alkoxy-substituted adducts were treated with BBr_3 to obtain dihydroxy derivatives followed by their oxidation to obtain the corresponding benzoquinones.[287]

Bis-*o*-quinodimethane generated *in situ* added two fullerene molecules[250] (Scheme 135).

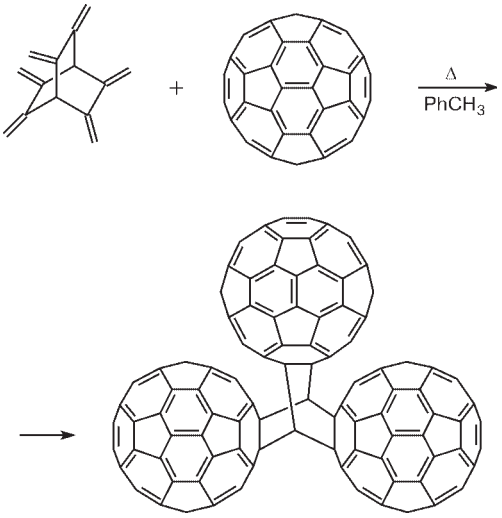
Scheme 135



Refluxing of a toluene solution of 2,3,5,6,7,8-hexamethylidenebicyclo[2.2.2]octane with an excess of fullerene afforded the Diels—Alder tris-adduct[288] (Scheme 136).

The generation of diene by treatment of the hepta-1,6-diyne derivative with trialkylsilane in the presence of $RhCl(PPh_3)_3$ was reported. The resulting cyclopenta-1,2-

Scheme 136

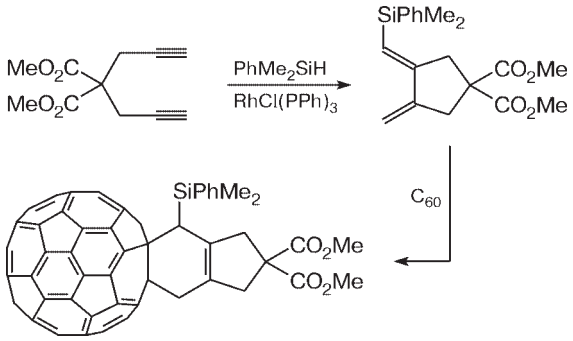


dimethylene derivative reacted with fullerene to give the Diels—Alder adduct in 71% yield. The diene that formed can also be isolated. The reaction of fullerene with the purified diene under comparable conditions afforded the cycloadduct in 58% yield[289] (Scheme 137).

Analogous results (without isolation of diene) were obtained with the use of dipropargyl ether and *N*,*N*-dipropargyltosylamine.[289]

Heating of the cobalt complex with η^5-bicyclo[3.2.0]hepta-1,3-diene in *o*-dichlorobenzene also gave rise to the diene fragment, which was captured by fullerene to give the Diels—Alder monoadduct and isomeric bis-adducts in 28 and 12% yields, respectively[290] (Scheme 138).

Scheme 137

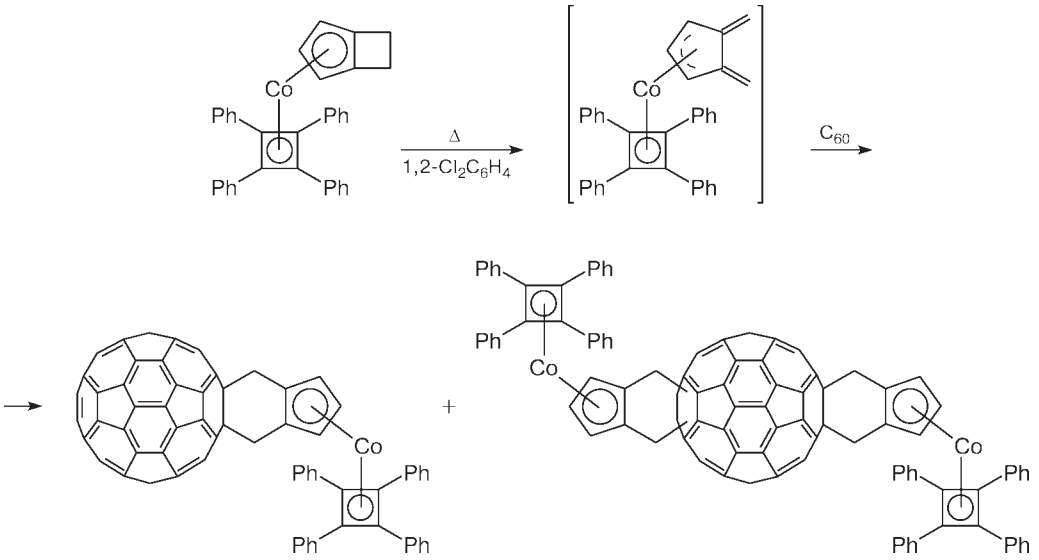


The iron carbonyl complex was used for the preparation of the cycloadduct with the cyclobutadiene derivative, which made it possible to obtain fullerene-fused bicyclo[2.2.0]hexanes,[291] which were inaccessible according to conventional procedure (Scheme 139).

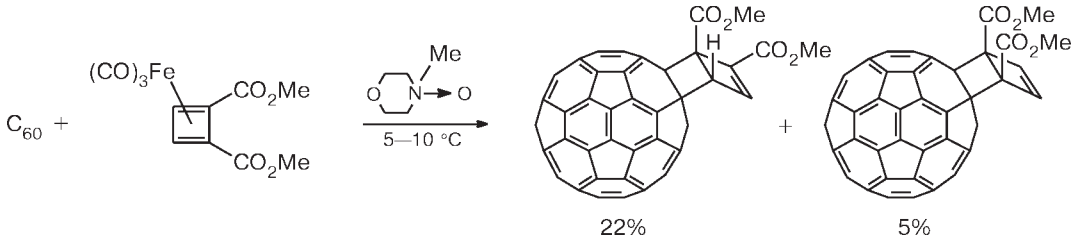
In the Diels—Alder reactions, fullerene acts as an electron-deficient dienophile. Consequently, electron-rich dienes are reagents of choice for [2+4]-cycloaddition. Numerous examples of such reactions are discussed above. At the same time, fullerene C_{60} reacts also with electron-deficient dienes, thus demonstrating the ability to be involved in the inverse electron demand Diels—Alder reactions. Thus, it was demonstrated that refluxing of a toluene solution of 3,6-diaryl-1,2,4,5-tetrazines with C_{60} produced fullerenopyridazines in 50—60% yields[292] (Scheme 140).

This reaction performed in the light yielded 4,15-dihydro derivatives. It was assumed that a small fraction of tetrazine was reduced in the light to give dihydrotetrazine,

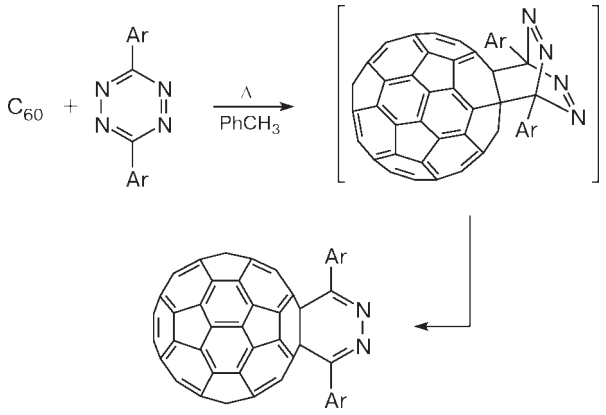
Scheme 138



Scheme 139

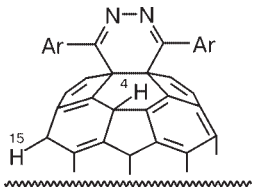


Scheme 140



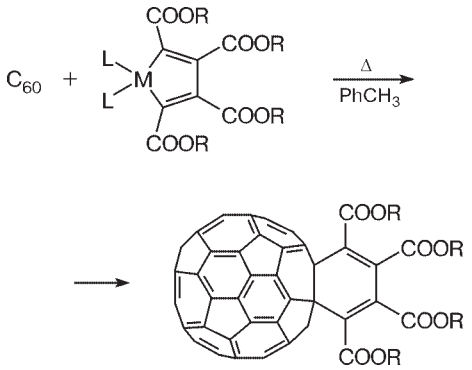
which, in turn, reduced the initially formed Diels—Alder adduct through electron transfer/proton transfer.

Unusual cycloaddition occurred in the case of electron-deficient metallacyclopentadienes used as the diene component[293] (Scheme 141).



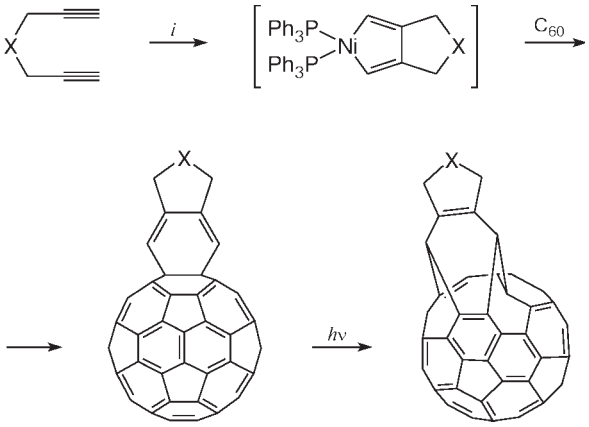
These reactions with platina- and palladacyclopentadienes bearing various ligands and ester groups afforded fullerenocyclohexadienes in yields from moderate to very good (71% when L is dimethylglyoximate, M = Pd, R = Me). In the case of the triphenylphosphine complex, the direction of the reaction depends on the solvent. Thus, [2+4]-cycloaddition was the main reaction in toluene containing 20% of DMSO (the yield of the adduct was 44%), whereas the reaction in toluene containing 20% of acetonitrile produced the $C_{60}Pd(PPh_3)_2$ complex as the major product (the yield was 20%).

Scheme 141

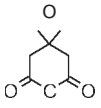


Metallacyclopentadienes can be generated *in situ* by the reactions of M^{II} with 1,6-diynes. Their subsequent reactions with fullerene afford fullerenocyclohexadienes. These reactions can also be described as [2+2+2]-cycloaddition (Scheme 142).

Scheme 142



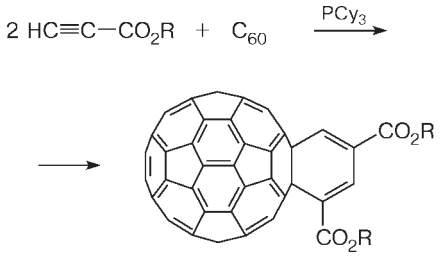
i. $(Ph_3P)_2NiCl_2$, PPh_3, Zn, toluene, Δ.

X	Yield (%)		X	Yield (%)	
	Diene	bis-Fulleroid		Diene	bis-Fulleroid
$C(CO_2Me)_2$	68	92	NTs	58	86
$C(CO_2Et)_2$	72	86	CH_2	66	
$C(COMe)_2$	75	84	O	47	
$C(SO_2Ph)_2$	53	90		70	

Similar [2+2+2]-cycloadd tion of ethyl and methyl propiolate to fullerene in the presence of tricyclohexyl-

phosphine yielded fullerenocyclohexadienes in which the ester groups are arranged in the "head-to-tail" fashion[294] (Scheme 143).

Scheme 143



Cy = *cyclo*-C_6H_{11}

The Diels—Alder reactions proceed generally by the concerted mechanism (path AC, Fig. 1). However, stepwise processes were observed in some cases giving rise to biradical (ABC or ADC)[295,296] or zwitterionic (AFC, AKC, AMC, or AHC) intermediates. The latter intermediates can be formed either directly (see, for example, Refs. 297—299) or through electron transfer as the first step of the process followed by the reaction of radical-cation and radical-anion fragments to produce zwitterions (for example, the path AEFC in Fig. 1). This mechanism of electron transfer was proposed, in particular, in the studies.[300—302] Taking into account the pronounced electron-deficient character of fullerene, this mechanism seems to be probable in the case of dienes possessing strong electron-donating properties. Actually, the reactions of fullerene with Danishefsky dienes, *viz.*, (1*E*)-1-methoxy-3-(trimethylsiloxy)butadiene and its (1*E*,3*Z*)-2,4-dimethyl

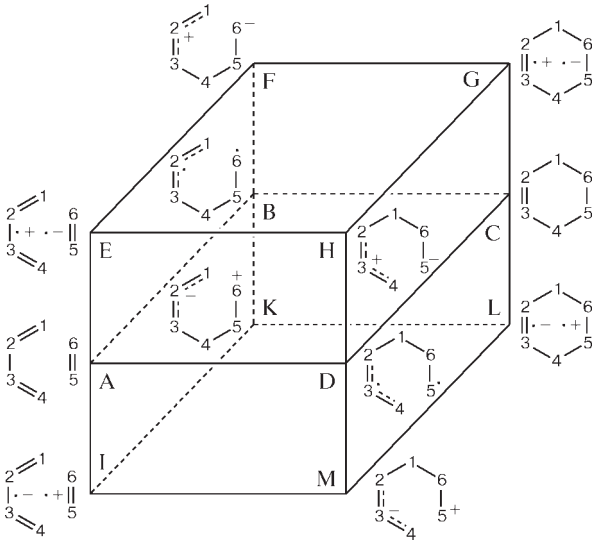
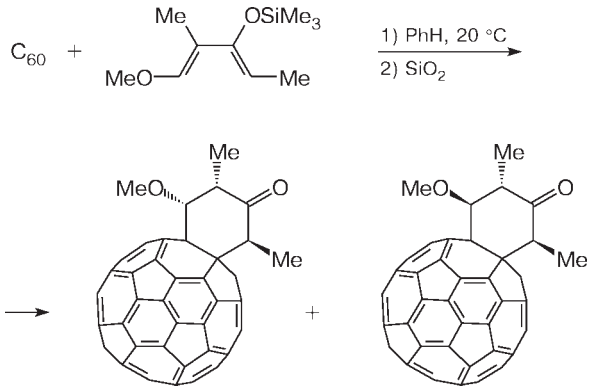


Fig. 1. Three-dimensional diagram reaction coordinate of the Diels—Alder cycloaddition .[305,306]

derivative, proceeded by the mechanism of electron transfer.[303,304] These reactions afforded mixtures of *trans*- and *cis*-adducts, with the *trans* isomer predominating. This fact is inconsistent with the concerted mechanism of [2+4]-cycloaddition (Scheme 144).

Scheme 144

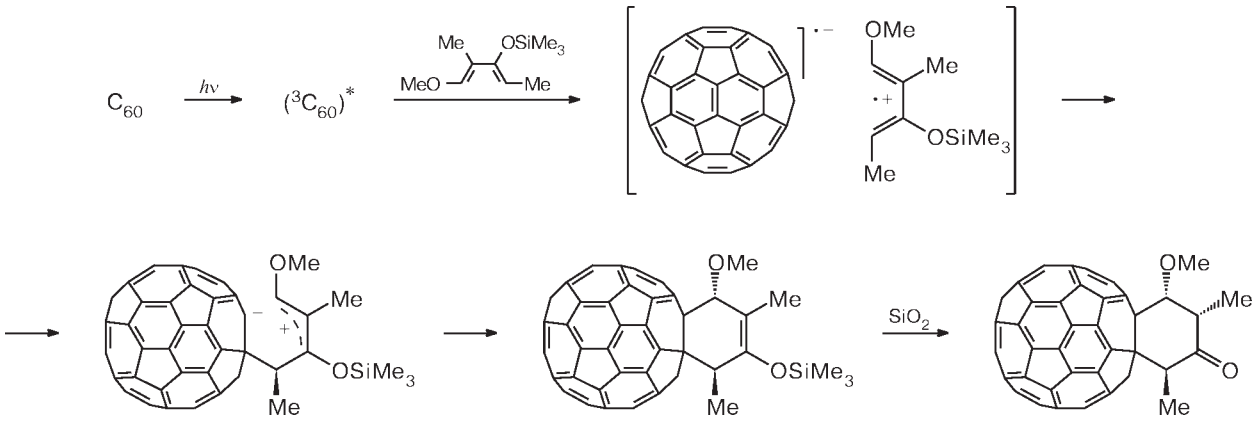


It can be concluded that the formation of "non-concerted" *trans*-adduct does not result from *cis—trans* isomerization because the proportion of the *trans*-adduct slowly decreased as the reaction time was increased (5% of the *trans*-adduct and 1% of the *cis*-adduct after 30 min; 13% of the *trans*-adduct and 3% of the *cis*-adduct after 1 h; 36 and 33%, respectively, after 6 h). As in the reactions of fullerene with substituted anthracenes, the latter reaction was accelerated under irradiation (18% of the *trans*-adduct after 30 min). This acceleration was attributed to the fact that the electron transfer from electron-rich diene to fullerene in the triplet state is more efficient as compared to its singlet form (Scheme 145).

The dimethyl derivative exhibits higher reactivity than (1*E*)-1-methoxy-3-(trimethylsiloxy)butadiene by itself (the reaction performed at room temperature for 6 h afforded the product in 24% yield), but this difference disappeared or even was reversed under the photochemical reaction conditions.[303]

The conclusion that the reaction proceeded by the mechanism of electron transfer (rather than with the simple formation of a biradical intermediate) was made based on the following facts. First, the spectrum of the fullerene radical-anion formed in the course of the reaction was measured.[303] The rate of decomposition of the triplet state of fullerene was found to be proportional to the concentration of the diene added. Second, the reaction rate agrees well with the value for electron transfer estimated from the oxidation and reduction potentials of the molecules involved in the reaction.[304] This fact excludes the possibility that the radical-anion is generated in a side reaction and unambiguously confirms that it is

Scheme 145

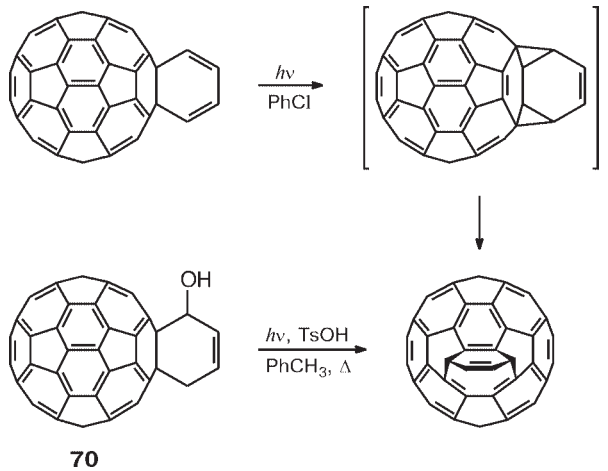


an intermediate of the process under consideration (see Fig. 1).

The stepwise mechanism involving electron transfer as the first step was proposed also for the above-discussed cycloaddition of 9-methylanthracene.[210]

Previously, it has already been demonstrated that the six-membered ring generated by cycloaddition can be used for the subsequent regioselective modification to produce fullerene derivatives possessing various properties. Among other directions of subsequent modifications of the Diels—Alder adducts, noteworthy is hydrolysis of the product of the reaction with 1-(trimethylsiloxy)butadiene followed by dehydration to produce fullereno[*e*]cyclohexadiene in 88% yield. The latter compound was isolated in the pure form[307] or as an iron tricarbonyl complex.[192] Besides, it was subjected to *in situ* photoinduced rearrangements giving rise to the bis-methanofulleroid structure[113] (Scheme 146).

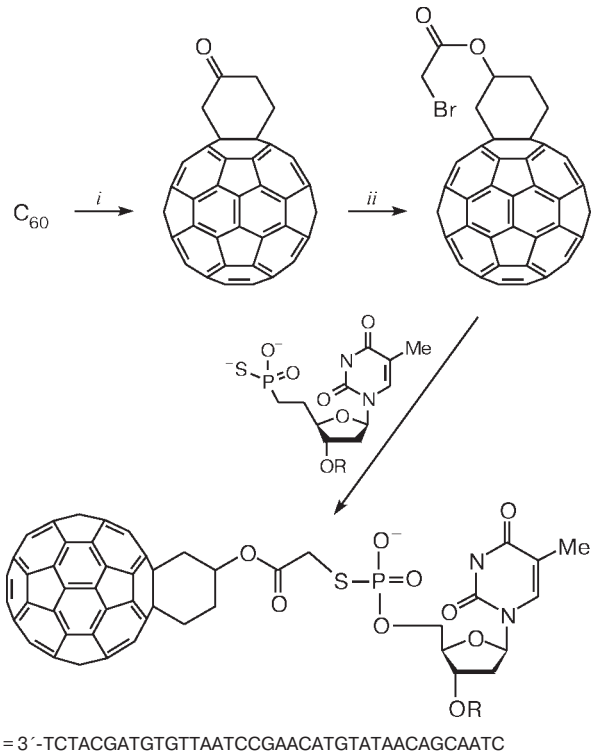
Scheme 146



70

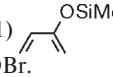
The same product was prepared by photolysis of compound **70** in the presence of *p*-toluenesulfonic acid.[113] This approach has synthetic advantages because com-

Scheme 147



R = 3′-TCTACGATGTGTTAATCCGAACATGTATAACAGCAATC

T is 2′-deoxythymidine-5′-phosphate,
C is 2′-deoxycytidine-5′-phosphate,
A is 2′-deoxyadenosine-5′-phosphate,
G is 2′-deoxyguanosine-5′-phosphate.

Reagents and conditions: *i*. 1)  , 2) H^+;
ii. 1) DIBAH, 2) $BrCH_2COBr$.

pound **70** can be prepared in good yield upon refluxing of a toluene solution of fullerene and inexpensive 1-(trimethylsiloxy)butadiene followed by acid hydrolysis of silyl ether.

Other simple transformations allowed the preparation of a broad spectrum of fullerene derivatives including fullerenonucleotides[308] (Scheme 147).

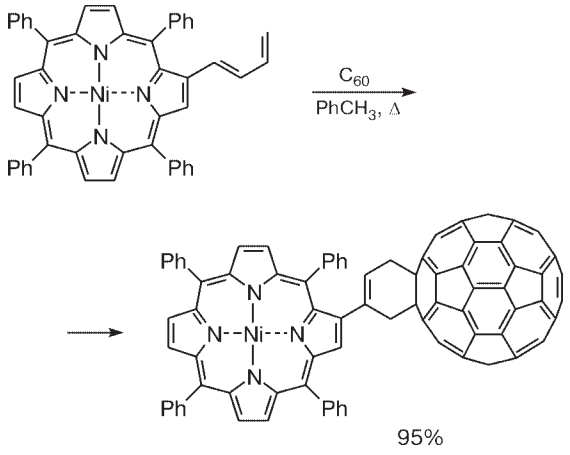
4.2. Properties and applications of Diels—Alder adducts of fullerene

As already discussed above, one of the most important properties of fullerene is its ability to be readily and efficiently (the quantum yield is close to unity) excited to the triplet state, which, in turn, generates singlet oxygen or oxidizes various electron-rich substrates in high yields. This oxidation can proceed by either an inter- or intramolecular mechanism, long-lived charge-separated states being often formed in the latter case. This intramolecular electron transfer in donor—spacer—acceptor systems is employed in various photoelectric devices. The use of these fullerene-based systems attracts considerable attention of researchers.[221,240,309—318] Fragments of tetrathiafulvalene and porphyrin are most commonly used as the donor component. Both rather simple and very complicated donor—fullerene systems were synthesized by [2+4]-cycloaddition reactions. For example, the simple Diels—Alder adduct of fullerene with 2-(butadien-1-yl)tetraphenylporphyrin was obtained in 95% yield. It should be noted that the reaction of this diene with fullerene was completed already in 2 h, whereas cycloadditions with *N*-phenylmaleimide or naphthoquinone was completed in 2 days[189] (Scheme 148).

As an example of a complex combination, we refer to the synthesis of "norbornylog-linked" donor-acceptor pairs wherein fullerene acts as acceptor[235,319—323] (Scheme 149).

The efficiency of various fullerene derivatives in such intramolecular electron transfer reactions depends on the nature of the spacer, the electron-withdrawing properties of the fullerene moiety, and the electron-donating properties of the second fragment (porphyrin, tetrathiafulvalene, *etc.*). Generally, Diels—Alder adducts[218,219,230,257,266,268,270,272,277,280,285,287,325,329—331] possess a somewhat more negative reduction potential

Scheme 148



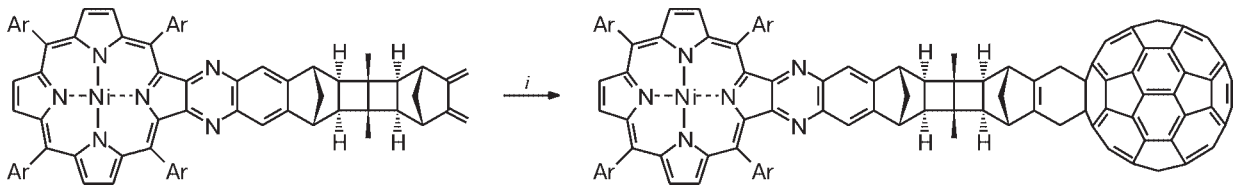
than fullerene by itself[219,266,268,277,280,325—328] due to saturation of the double bond involved in cycloaddition.[324]

Electron-donating groups in fullerene adducts are, in turn, oxidized at more positive potentials than those in the starting compounds. Nevertheless, the differences in the oxidation and reduction potentials for the donor—spacer—fullerene systems are generally rather small (0.9 V),[260,280] which ensures the efficiency of intramolecular photoinduced electron transfer and allows the use of these compounds as photoelements. The possibilities of the application of porphyrin derivatives of fullerene in photoelectronic devices were discussed in recent reviews.[332,333]

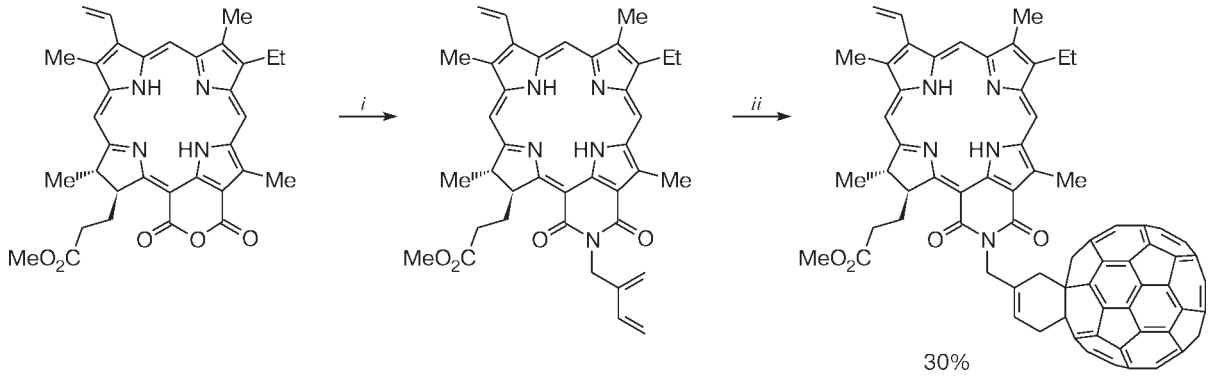
Many fullerene—porphyrin systems possess a rather long-lived charge-separated excited state,[240,310,320,334,335] whereas the use of unsymmetrical chlorine derivatives as the donor leads to rapid quenching of the excited state both in the case of the zinc(II) complex and with the use of chlorine as a free base.[336] The synthesis of the above-mentioned complex involves the insertion of the acetylene substituent into the starting chlorine (methyl ether of purpurin-18). Metathesis leads to transformation of this function into the diene fragment, which reacts with fullerene upon refluxing in toluene (Scheme 150).

Unlike the above-mentioned examples, the adducts, which are generated by [2+4]-cycloaddition of fullerene to the nickel complexes of phthalocyanine and hemi-

Scheme 149



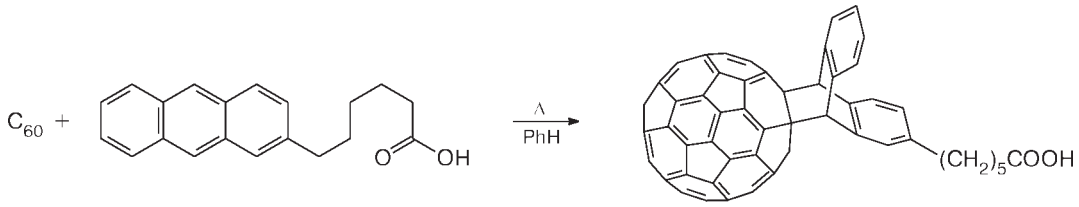
Scheme 150



Cy = *cyclo*-C_6H_{11}

Reagents and conditions: *i*. 1) $NH_2CH_2C{\equiv}CH$, 2) C_2H_4, $Cl_2(PCy_3)_2Ru{=}CHPh$; *ii*. C_{60}, PhMe, Δ.

Scheme 151



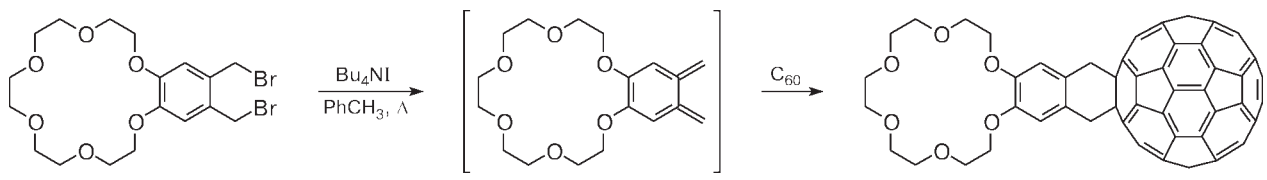
porphyrazine, show no substantial effect of the electron-withdrawing fragment on the properties of the donor component and *vice versa*.[337] This difference was accounted for by an increase in the length of the carbon chain that links the electron-withdrawing and electron-donating fragments. Actually, fullerene, which is linked to the porphyrin moiety through the elongated norbornane spacer ("norbornylog"), was also demonstrated[319] to have no effect on the properties of porphyrin and *vice versa*. At the same time, the phthalocyanine-fullerene system bearing a short spacer is characterized by essential interaction between the donor and the acceptor.[338] The effect of the length of the spacer carbon chain on the efficiency of electron transfer between fullerene and ferrocene was analyzed in detail.[90]

Fullerene derivatives find important use in the preparation of ultrathin Langmuir—Blodgett films. Fullerene-containing amphiphylic monomers were produced by the Diels—Alder reaction of fullerene with 6-(2-anthryl)hexanoic acid[339] (Scheme 151).

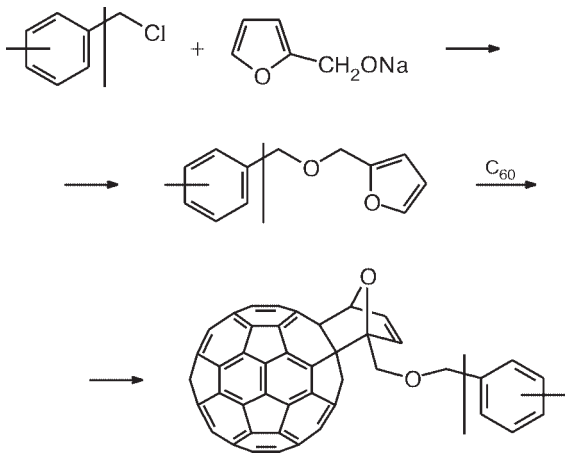
Langmuir—Blodgett films were also prepared with the use of the fullerene derivative of crown ether, which was synthesized by the reaction of fullerene with *o*-quinodimethane generated from 4,5-bis(dibromomethyl)benzo-18-crown-6 [255] (Scheme 152).

Another approach to new materials is to synthesize polymers modified by fullerenes. These polymers can be prepared by inserting fullerene into a polymeric matrix through a physical adsorption, by polymerization of fullerene-containing monomers, or by chemical modification of the polymer, including cycloaddition reactions. Thus, chloromethylated polystyrene—divinylbenzene copolymer (Merrifield resin) was treated with furfuryl alcohol in the presence of sodium hydride to obtain the furan-functionalized polymer. Stirring of the latter with fullerene at room temperature afforded a polymer containing 55 mg of fullerene per gram of the resin (Scheme 153).[224] The Diels—Alder reaction using the polymer modified with cyclopentadiene was somewhat less efficient.[225]

Scheme 152

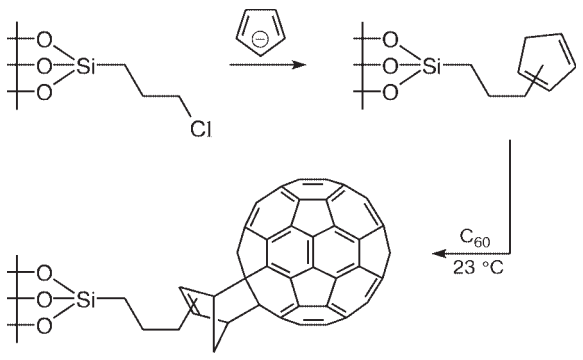


Scheme 153



Silica gel and various aluminosilicates find increasing use for immobilizing functional groups on a support. The Diels—Alder reaction of fullerene with cyclopentadiene anchored to the surface of a support was used for this modification of silica gel[340] (Scheme 154).

Scheme 154



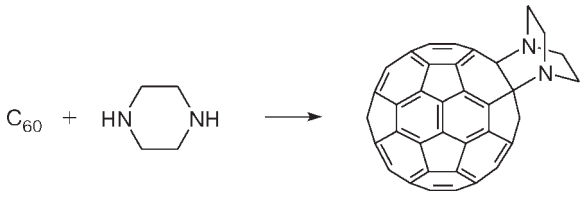
As in the case of most of substituted cyclopentadienes, the reaction is reversible. Thus, refluxing in toluene induced the retro-reaction with regeneration of cyclopentadiene-functionalized silica gel. After cooling of the solution to room temperature, fullerene binding was resumed.

4.3. Cycloaddition of diamines

Fullerene exhibited the unusual behavior in the reactions with piperazine, cyclohexane-1,2-diamine, and other 1,2-diamines to produce the product of nonconcerted cycloaddition of two amino groups at the 6,6-bond[341—344] (Scheme 155).

As in the case of the Diels—Alder reactions, cycloaddition of an excess of diamines afforded a mixture of bisadducts.[341]

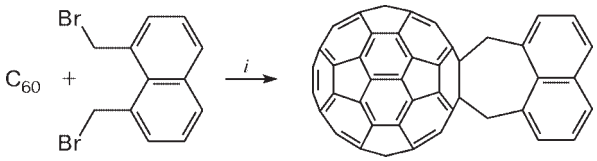
Scheme 155



5. [2+5]-Cycloaddition

Although [2+5]-cycloaddition reactions of fullerenes have gained much less acceptance, several examples were reported. Thus, it was found that the reaction of [60]fullerene with 1,8-bis(bromomethyl)naphthalene in refluxing benzene in the presence of NaI and 18-crown-6 gave rise to the corresponding fullerenocycloheptane in 75% yield (Scheme 156).[345]

Scheme 156



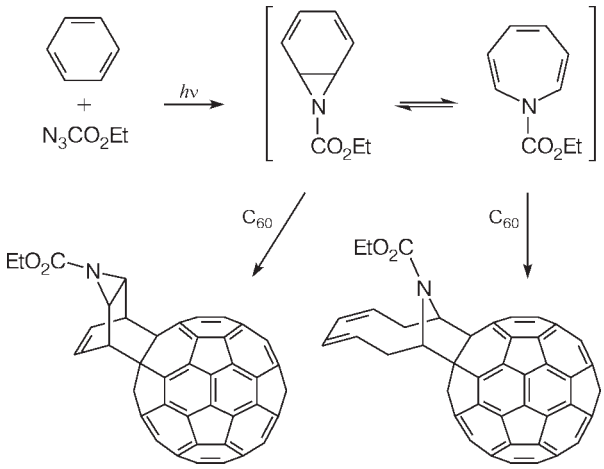
i. 18-Crown-6, NaI, benzene, Δ.

Like the reactions of 1,2-bis(bromomethyl)benzene derivatives, the latter reaction proceeds through the formation of highly reactive diene, which rapidly adds at the most reactive 6,6-bond of fullerene. The resulting cycloadduct is similar in properties to the Diels—Alder adducts. The UV spectrum in dichloromethane shows the characteristic absorption at 433 nm. The ^{1}H NMR spectrum has signals of the methylene protons at δ 4.62 and 6.24. Such splitting is untypical of [2+4]-cycloadducts but is observed in the spectrum of methanofullerene $C_{61}H_2$ in which the signal for the proton located above the five-membered ring of fullerene is observed at much lower (by 3.48 ppm) field than the signal for another proton.[346—348] The ^{13}C NMR of this adduct also shows characteristic signals for the methylene carbon atom (at δ 51.22) and the carbon atoms of the 6,6-bond of fullerene (at δ 67.53). The electrochemical behavior of this adduct is similar to that of fullerene C_{60} and its cycloadducts (the first three reduction waves at −1.150, −1.540, and −2.090 V *vs.* Fc/Fc^+, MeCN—PhMe, are reversible; the fourth wave at −2.550 V is irreversible; reduction proceeded at more negative potentials than that in the case of fullerene by itself).

6. [2+6]-Cycloaddition

[2+6]-Cycloaddition reactions of fullerenes remain poorly studied. We found only one example of these reactions. Thus irradiation of a mixture of fullerene and ethyl azidoformate in benzene afforded a mixture of [2+6]- and [2+4]-cycloaddition products between fullerene and *N*-ethoxycarbonylazepine generated through the reaction of nitrene with benzene[349] (Scheme 157).

Scheme 157

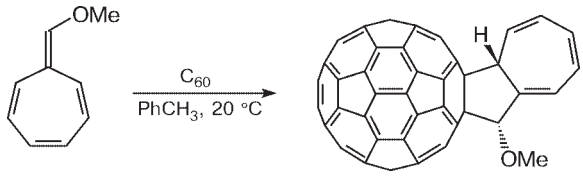


Noteworthy is the substantial difference in the behavior of nitrenes and carbenes in these reactions. As discussed above, the reactions of esters of diazoacetic acid performed under similar conditions gave [2+4]-cycloaddition products and small amounts of [2+1]-adducts.[231] However, the [2+6]-cycloadduct was not detected. Another procedure for the carbene generation (decomposition of diazo compound with rhodium acetate) has no effect on the absence of the highest cycloaddition product. This difference is determined by both the equilibrium between two isomeric forms of the adduct of carbene (nitrene) with (substituted) benzene and the difference in the reactivity of these forms. Both isomeric forms of cycloheptatriene reacted with fullerene,[229] but both reactions gave rise to the [2+4]-cycloaddition products. Apparently, the change in the direction of the reaction (the formation of the [2+6]-cycloaddition product) in the case of the azepine derivative results from the effect of the nitrogen atom on the properties of the frontier orbitals of (substituted) cycloheptatriene.

7. [2+8]-Cycloaddition

The insertion of the methylene substituent at position 7 of cycloheptatriene leads to a further change in the direction of the reaction with fullerene. Thus, the reaction of C_{60} with 7-methoxymethylenecyclohepta-1,3,5-triene was classified as [2+8]-cycloaddition.[350] It should be noted that the formation of the fullerenocyclopentane derivative in this reaction can also be considered as a consequence of the above-discussed [2+3]-cycloaddition between fullerene and the zwitterionic form of the reagent (Scheme 158).

Scheme 158



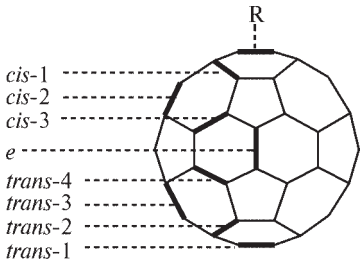
8. Polycycloaddition

In early studies on the chemistry of fullerene, prominence was given to examination of monocycloaddition processes, the development of preparative procedures for the synthesis of monocycloadducts, and comprehensive investigations of their chemical, physicochemical, and other properties. In recent years, the more complicated field of the chemistry of fullerene, *viz.*, polyaddition processes, has attracted increasing attention. Adequately constructed polyadducts of C_{60} with particular three-dimensional structures can serve as potent biologically active compounds and as the basis for the preparation of new modern materials. However, the unique characteristic feature of C_{60} is that polyaddition can afford a large number of adducts (including isomeric) even with the use of one reagent because [60]fullerene has, for example, 30 double 6,6-bonds capable of being involved in addition reactions. To construct three-dimensional structures based on C_{60}, it is necessary to control the regio- and stereochemistry of polyaddition, which is the prime objective of these studies. Presently, the chemistry of fullerene oligocycloadducts includes data on almost the complete spectrum of these derivatives from bis- to hexakis-adducts (data on higher adducts are scarce).

8.1. Bis-cycloadducts

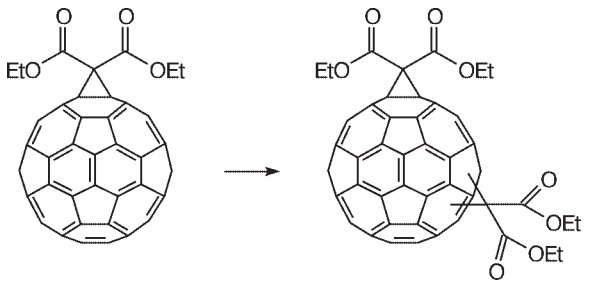
For the purpose of the correct discussion of the regiochemistry of bis-addition, a convenient, simple, and clear nomenclature was proposed for the relative arrangement of addends[351] analogous to the notation of the *ortho*, *meta*, and *para* positions used in the chemistry of benzene.

It should be noted that most of procedures for the synthesis of monoadducts are also suitable for repeated additions to C_{60}. However, in most cases the non-controlled successive polyfunctionalization of the carbon



sphere gives rise to considerable difficulties due to the formation of mixtures of regioisomeric adducts, which requires cumbersome chromatographic separation. The problem of the formation of such mixtures of adducts upon nucleophilic addition to C_{60} is best exemplified by successive double cyclopropanation by the Bingel reaction with diethyl 2-bromomalonate in the presence of a base. Of eight possible bis-adducts, seven isomers were isolated by chromatography[352] (Scheme 159).

Scheme 159



cis-2	0.9%
cis-3	2.5%
e	15.5%
trans-4	3.7%
trans-3	12.0%
trans-2	5.3%
trans-1	0.8%

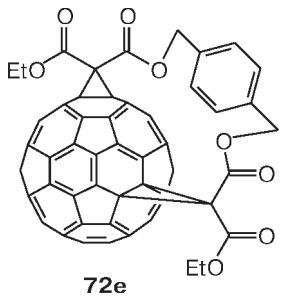
It should be noted that the structure assignments of isomeric bis-adducts[353] as well as of higher polyadducts[354] are convenient to make using excited-state EPR spectroscopy and time-resolved EPR spectroscopy[355,356] (along with UV-Vis and NMR spectroscopy). Moreover, ^{3}He NMR spectroscopy gives excellent results in the determination of the ratio of isomeric bis-adducts and their identification with the use of inclusion compounds (^{3}He@C_{60}) as the substrate.[357]

The unexpected discovery of electrochemical isomerization of fullerene bis-adducts through migration of the cyclopropane rings over the surface of the carbon sphere[358] can change the situation concerning the quantitative distribution of isomers. Such unprecedented "walk on the sphere" was observed for six regioisomeric bis-malonate adducts. The distribution of the isomers was found to be virtually unchanged whatever the isomer was subjected to electrolysis. This fact indicates that the process is thermodynamically controlled. Of special note are rather high contents of the *trans*-2 and *trans*-1 isomers, which are generally obtained in small amounts (see Scheme 159 and Ref.[352]).

Starting isomer	Isomer content (%)				
	e	*trans*-4	*trans*-3	*trans*-2	*trans*-1
cis-2	23	5	8	52	12
cis-3	22	6	10	51	11
e	26	9	12	44	9
trans-4	23	10	12	47	8
trans-3	23	9	12	46	10
trans-2	22	6	9	53	10

However, the principal way out was found using the strategy of "tether-directed remote functionalization" proposed in 1994.[352,359] Thereafter, template syntheses became elegant procedures for regio- and stereoselective polyfunctionalization of fullerene. The review devoted to these synthetic procedures[359] surveyed covalent templates, such are addends, which can be reversibly removed, and spacers used for achieving a wide diversity of spatially functionalized building blocks. It should be noted that the sizes, structural characteristics, and conformations of the spacers unambiguously determine the mutual arrangement of addends upon polyfunctionalization. For example, double addition of bis(2-bromomalonates) **71a—d** containing directing tethers by the Bingel reaction proceeded with high regioselectivity to give *cis*-2-isomers as the only reaction products[360] (Scheme 160).

The use of the *para*-xylylene tether in bis(2-bromomalonate) **71e** led to the regioselective formation of *trans*-4-isomeric bis-adduct **72e** (33%).

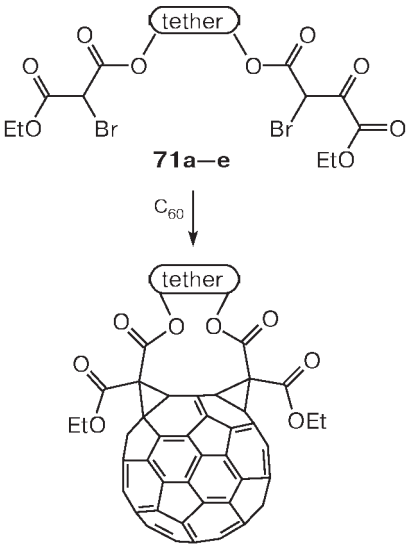


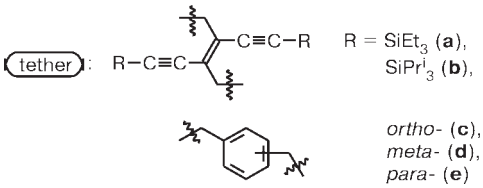
72e
trans-4

Analogous results were obtained with the use of other β-ketoesters.[361]

Theoretically, each cyclic regioisomer must be produced as a mixture of diastereomers depending on the arrangement of the substituents at the bridgehead position of the methylene groups (*in-in, in-out,* or *out-out*). In the case of bis-adducts **72a—e** bearing a simple symmetrical spacer, 37 stereoisomers and constitutional isomers

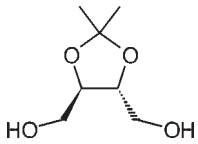
Scheme 160





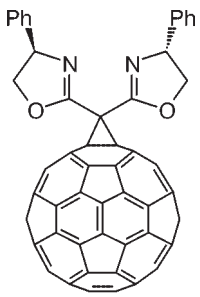
Compound	72a	72b	72c	72d
Yield (%)	16	10	33	32

can be formed. However, bis-adducts were isolated as pure achiral compounds or simple racemic mixtures, *i.e.*, in the presence of a spacer, the second addition by the Bingel reaction proceeded not only regio- but also stereospecifically. Actually, the identical *out-out* arrangement was observed in all bis-adducts. This arrangement in compound **72c** was confirmed by X-ray diffraction analysis.[361] The above-described methodology allowed the preparation of enantiomerically pure *cis*-2-bis-adducts with the use of bis(2-bromomalonates), which were synthesized from commercially available chiral diols.[362]



(+) and (–) isomers

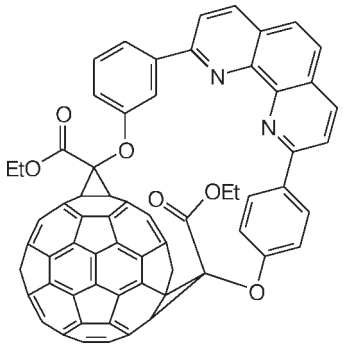
The repeated cyclopropanation with diethyl bromomalonate using chiral methanofullerenes as substrates allows the preparation of enantiomerically pure bis- and tris-adducts by simple separation on standard chromatographic stationary phases. For example, C_2-symmetrical (*R,R*)-bis(oxazolyl)methano[60]fullerene was used for these purposes.[363]



R,R

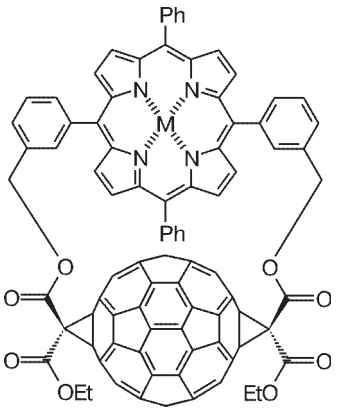
It should be noted that even in the case of addition of achiral addends, the chirality of polyadducts can be caused by the chirality of the π-system of C_{60} and the chiroptical properties can be determined by a diastereomeric fullerene chromophore. For example, bis-, tris-, and hexakis-adducts of fullerene with achiral addends were separated by HPLC on the Whelk-01 chiral phase.[364]

The use of the large-sized phenanthroline tether made it possible to prepare the first *trans*-3-bis-adduct **73** with the *in-out* arrangement of the substituents.[362]



(±) **73** *trans*-3 *in-out*

A spatially even more extended tether, such as the porphyrin fragment, enables one to direct the second addition in the Bingel reaction to the even more remote *trans*-1 and *trans*-2 positions.[317,365—367] This regioselective bis-cyclopropanation afforded C_2-symmetrical [60]fullerenoporphyrin dyes with pronounced electronic interaction between two folded π-π-chromophores.

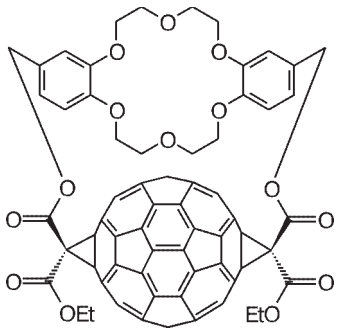


trans-1

M = 2 H, Zn

Regioselective macrocyclization of C_{60} with bis-malonate containing a spacer based on dibenzo-18-crown-6 also afforded the only planar-chiral *trans*-1 diastereoisomer in a yield of higher than 30%.[368]

The general methodology of bis-cyclopropanation was used also for the preparation of highly soluble fullerene



trans-1

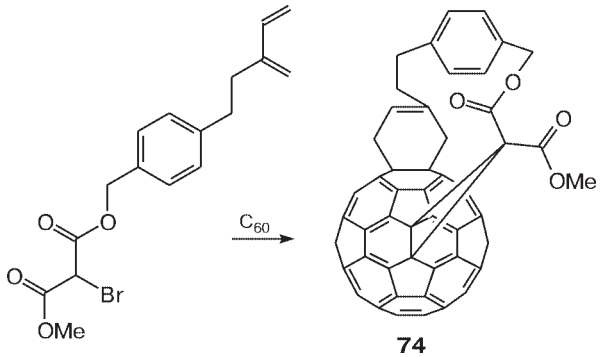
dendrons, which can form stable Langmuir—Blodgett films at the air—water interface.[369—371]

The versatility of the above-described method can also be demonstrated with the preparation of the first [2]-catenane-containing *trans*-4-fullerene bis-adduct.[372]

The complete regioselectivity was achieved in the synthesis of *e*-bis-adduct **74** by the combined double addition of a conjugate containing the corresponding anchored active groups (bromomalonate and diene) to C_{60} by the Bingel and Diels—Alder reactions[373] (Scheme 161).

Unusual bis-cyclopropanation, which proceeded at two double bonds of the same six-membered ring (in all the above-considered examples, bis-cyclopropanation occurred at different six-membered rings of fullerene), was observed in the reaction of C_{60} with ethyl propiolate in the presence of triphenylphosphine.[374] The mechanism of the transformation is shown in Scheme 162. It should be noted that the product of [2+2]-cycloaddition of propiolate to C_{60}, *viz.*, cyclobutenofullerene, was formed along with the bis-adduct.

Scheme 161



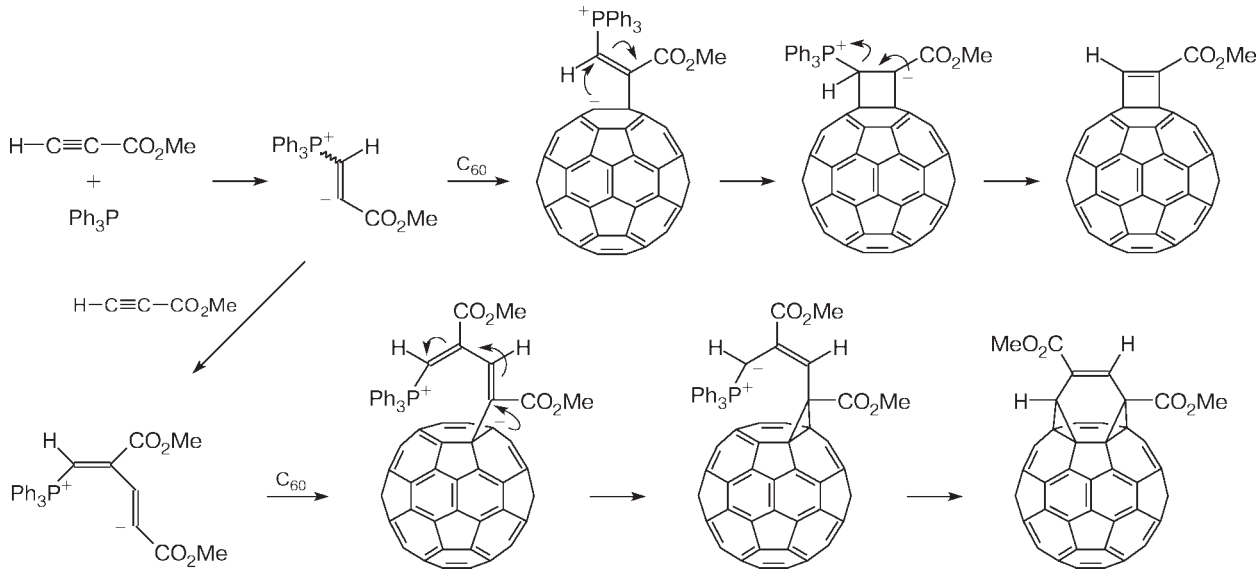
74

In the case of bis-cyclopropanation, functionalization at one ring of fullerene is the exception rather than the rule. At the same time, this direction of bis-addition in the reactions with bis-azides becomes dominant virtually irrespective of the length of the chain separating two azide groups,[375—377] the addition occurring at two 6,5-bonds to form fulleroid structures. Thus, refluxing of a xylene solution of C_{60} with diethyl diazidomalonate gave rise to the 1:1 adduct with the structure of bis-azafulleroid in 65% yield[378] (Scheme 163).

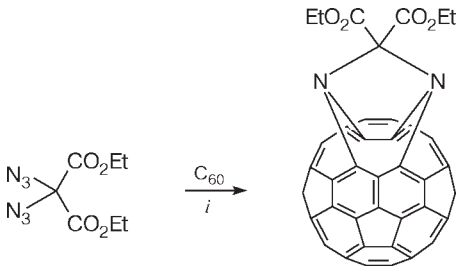
The regiochemistry of bis-addition remains unchanged when the azide functional groups are separated by two or three methylene groups. Thus, the bis-addition still proceeds at two 6,5-bonds of the same five-membered ring of fullerene[377] (Scheme 164).

The reactions of C_{60} with chiral 1,4-*tert*-alkoxy-2,3-bis-azidobutanes afforded the corresponding chiral bis-azafulleroids (2*R*,3*R*)-**75a**, (2*S*,3*S*)-**75a**, (2*R*,3*R*)-**75b**, and

Scheme 162

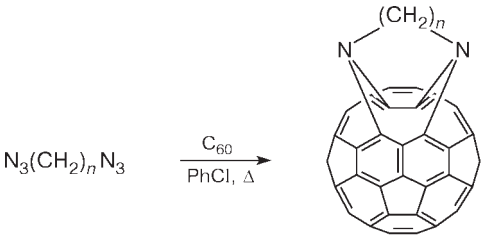


Scheme 163



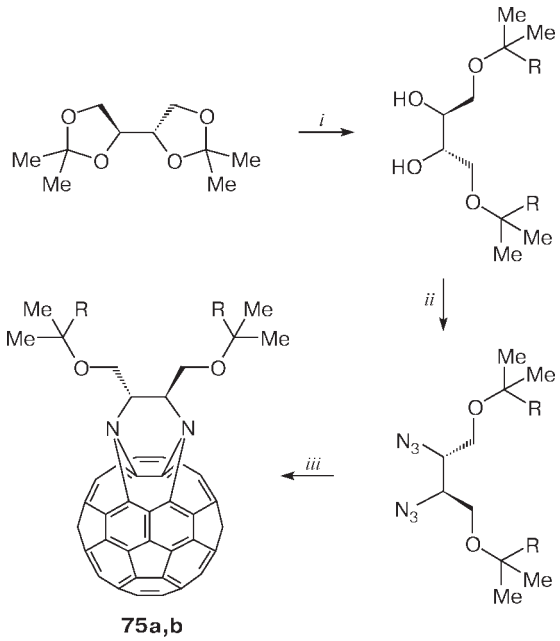
i. Xylene, Δ, 24 h.

Scheme 164



n = 2 (53%), 3 (31%)

Scheme 165



R = Me (**a**), Ph (**b**)

Reagents and conditions: *i*. RMgX; *ii*. 1) MsCl, 2) LiN_3, 15-crown-5; *iii*. C_{60}, PhCl, Δ.

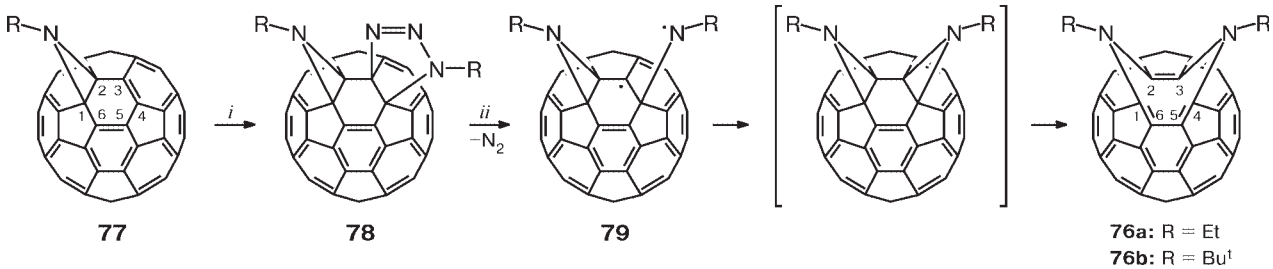
(2*S*,3*S*)-**75b** in 54, 49, 56, and 51% yields, respectively. Their enantiomeric pairs show mirror curves in the circular dichroism spectrum[376] (Scheme 165).

The corresponding fullerene-containing derivatives of *p-tert*-butylcalix[4]crowns capable of forming exohedral complexes with the Li^+, Na^+, and Ag^+ cations have analogous bis-azafulleroid structures.[378,379]

Bis-functionalization of C_{60} with monoazides (ethyl and *tert*-butyl azidoformates) produced not only regioisomeric [6,6]-closed bis-iminofullerenes but also *cis*-1 isomers, which were the first fullerene derivatives with the open [6,6]-transannular bonds[380] (Scheme 166).

Compounds **76a,b** were prepared with rather high regioselectivity starting from monoiminofullerene **77**. In these reactions, intermediates **78** were formed *via* [2+3]-cycloadditions in the course of which the negatively polarized nitrogen atom (R—*N*—N_2) formed a bond with the most positive carbon atom (C(4)). This bond polarization was confirmed by AM1 calculations. Thermal elimination of N_2 afforded biradical intermediate **79**. Due to localization of the first addend in the same six-membered ring, the usual delocalization of the spin density in this ring (*i.e.*, the transfer of the spin density to the C(5) atom) is made impossible, and recombination of the radical can take place only if it is located at the C(3) atom. Consequently, the formation of the tropilidene-like (1,2,4,5-bis-imino[60]fullerene) structure prevails. The subsequent intramolecular retro-Diels—Alder reaction (2π-2σ isomerization) gave rise to compounds **76**.

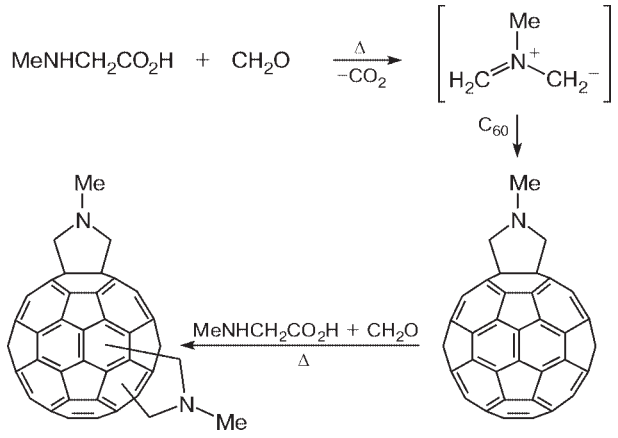
Scheme 166



Reagents and conditions: *i*. 2 equiv. of N_3CO_2R, 1-chloronaphthalene, 40 °C, 4 days; *ii*. toluene, Δ, 30 min.

Along with the Bingel reaction and polyaddition of azides, other known procedures for functionalization of the carbon sphere, for example, the Prato reaction (see Section 2.2), were also used for the synthesis of fullerene bis-adducts. Actually, repeated 1,3-dipolar cycloaddition of azomethine ylide to *N*-methylfullerenopyrrolidine afforded an isomeric mixture of bis-adducts. Six of eight possible bis-adducts were isolated and characterized by spectroscopic data[381] (Scheme 167).

Scheme 167

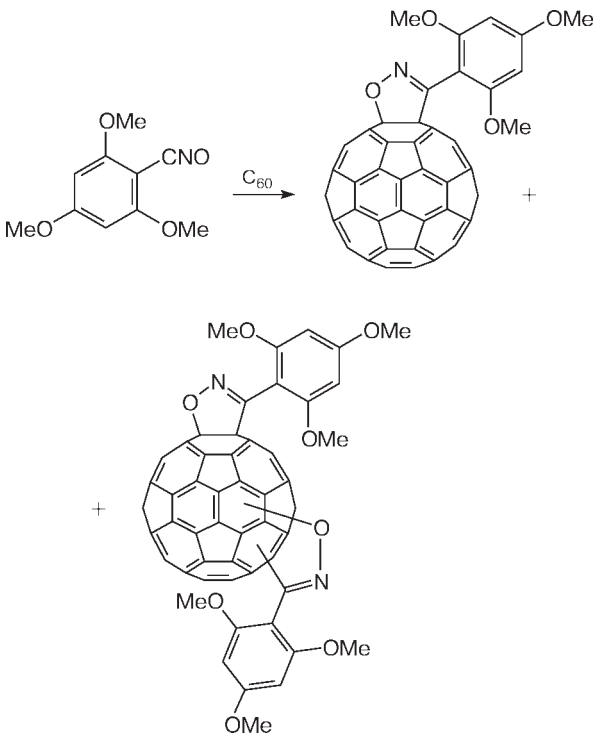


The structure assignments of isomeric fullerenobis-pyrrolidines were based on (1) correlation of their molecular symmetry with the ^1H and ^{13}C NMR spectra; (2) comparison of their electronic spectra with the spectra of bis-methanofullerenes, and (3) consideration of deshielding of the protons of the methylene and *N*-methyl groups in the ^1H NMR spectra. One would expect that the latter reactions will afford isomers in a ratio different from that obtained in the case of bis-cyclopropanation by the Bingel reaction because these reactions proceed by different mechanisms. Actually, the Bingel reaction yielded the *e*- and *trans*-3 isomers as the major products, whereas the Prato reaction (according to HPLC data) afforded the *trans*-2-, -3-, and -4-isomers and the *cis*-3-isomer as the major products in a ratio of 20 : 24 : 18 : 25.

Water-soluble fullerenobis(pyrrolidinium) salts were prepared analogously. These salts possess stronger electron-withdrawing properties than fullerene by itself (this was demonstrated in the study of their radical and light-induced reduction) and proved to be excellent free-radical scavengers, including the reactions with $O_2^{\bullet -}$ in aqueous media.[382]

1,3-Dipolar cycloaddition of 2,4,6-trimethoxybenzonitrile oxide to C_{60} afforded a complex mixture of isomeric fullerenobis(isoxazolines) along with the monoadduct. Of 20 possible bis-adducts, 16 compounds were characterized[383] (Scheme 168).

Scheme 168

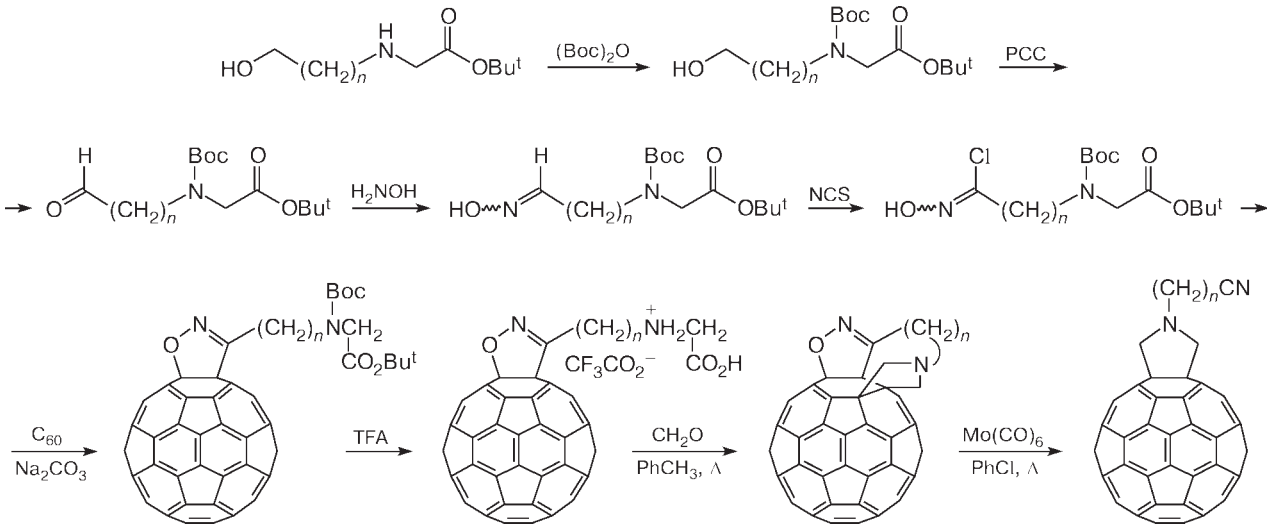


The tether-directed tandem addition of nitrile oxide and azomethine ylide produced predominantly *cis*-1-bis-adducts. The subsequent reductive ($Mo(CO)_6$ or $Bu^i_2LiAlH_2$) removal of the isoxazoline fragment gave rise to *N*-cyanoalkylfullerenopyrrolidines[384] (Scheme 169).

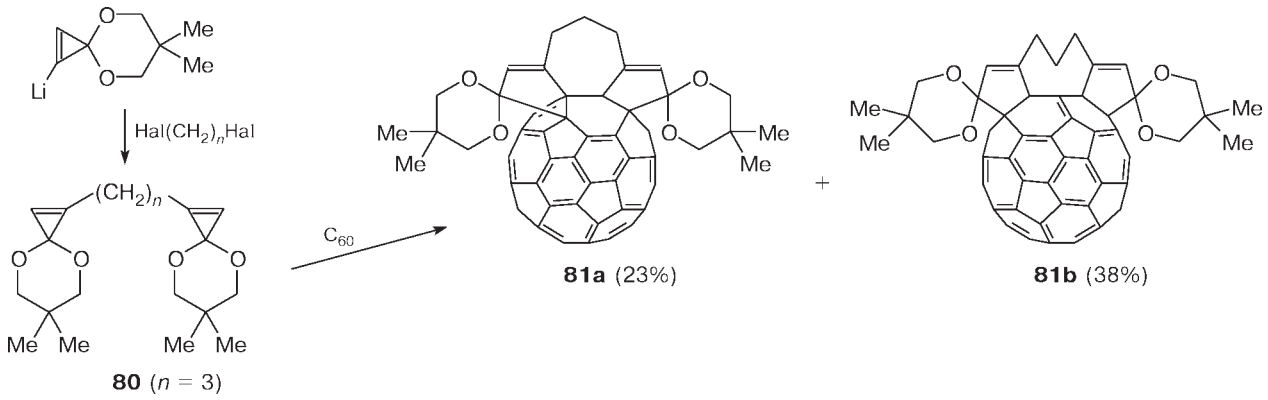
With the aim of performing double functionalization of [60]fullerene for the one-step construction of tricyclic carbocycles on the fullerene sphere, new tris-annelating reagents **80** were developed.[385,386] These reagents contain simultaneously two cyclopropenoneacetals tethered by the methylene chains of different length. When subjected to thermolysis in the presence of C_{60}, reagents **80** are involved in double regio- and stereoselective [2+3]-cycloaddition, the selectivity of the process being the function of the tether structure. The unique property of these reagents is that thermolysis leads to reversible generation of a controlled amount of vinylcarbene and, consequently, hinders its intramolecular dimerization. Double cycloadditions were performed by simple heating of a mixture of reagents **80** and C_{60} in dry 1,2-dichlorobenzene in the presence of 4 Å molecular sieves under a stream of nitrogen. The reaction products were isolated by flash chromatography. The use of reagent **80** containing the three-unit methylene chain ($n = 3$) led to the formation of a mixture of two C_s-symmetrical bis-adducts **81a** (*cis*-1) and **81b** (*cis*-2) in 23 and 38% yields, respectively (Scheme 170).

An analogous result, *viz.*, the formation of *cis*-1 bis-adduct **82** (34%), was obtained with the use of reagent **80**

Scheme 169



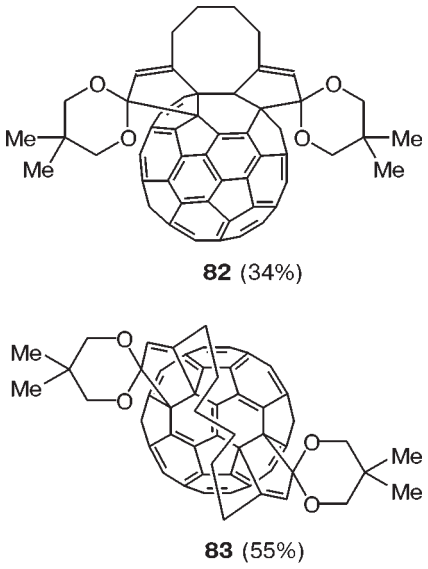
Scheme 170



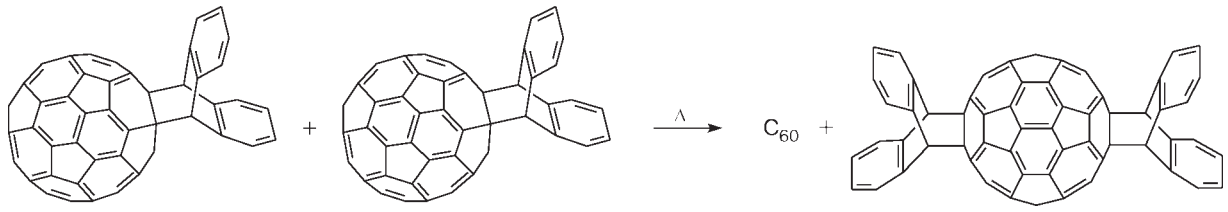
with $n = 4$. In the case of the longer (six-unit) methylene tether ($n = 6$), more remote functionalization was achieved to give C_2-symmetrical bis-adduct **83** in rather high yield (55%).

The application of the Diels—Alder reaction to the synthesis of [60]fullerene bis-adducts was also reported. Thus, heating of the monoadduct of fullerene with anthracene in solution led to its decomposition into fullerene and anthracene.[205] Unlike thermolysis in solution, solid-phase heating of this adduct at 180 °C for 10 min resulted in 96% conversion of the monoadduct to form a 1 : 1 mixture of fullerene and the only bis-adduct with the *anti* arrangement of the addends[252] (Scheme 171).

The fact that the reaction performed under these conditions afforded exclusively the *anti* adduct is attributed to the characteristic features of the crystal packing of the starting compound in which the anthracene moiety of one molecule is located in the *anti* position with respect



Scheme 171

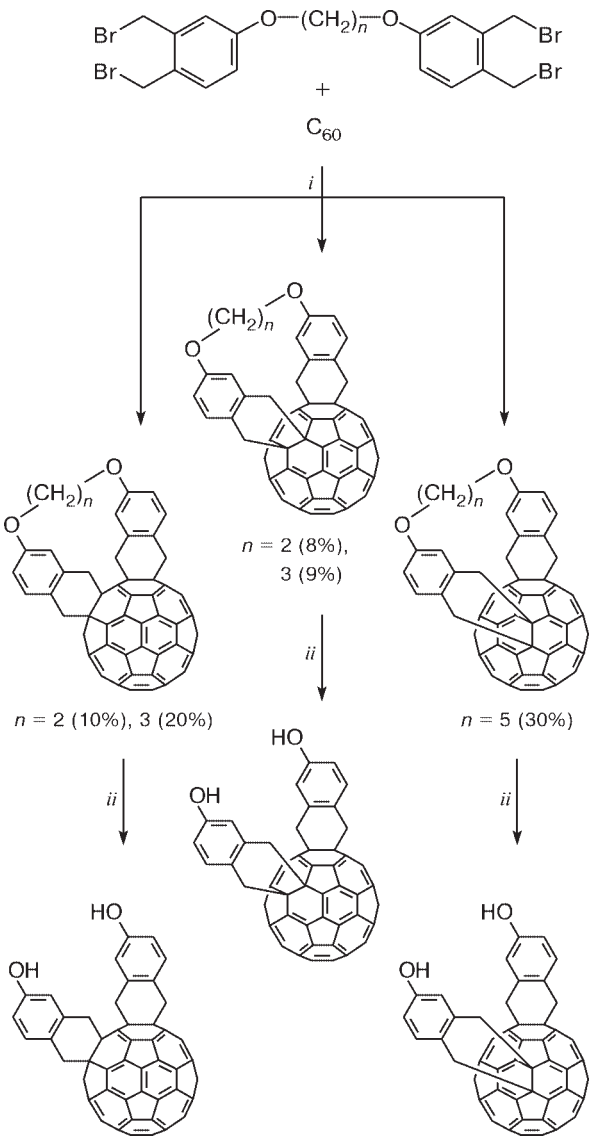


to the same fragment of the adjacent molecule. Such arrangement restricts the possibility of anthracene, which is eliminated in the course of the retro-reaction, to be involved in the reaction with the most closely-spaced and accessible 6,6-bond. Solid-phase thermolysis is an efficient procedure for the regioselective formation of the bis-adduct with the *anti* arrangement of the substituents because the reactions of fullerene with an excess of various dienes in solutions generally afford mixtures of addition products. Thus, the reaction of the monoadduct of anthracene and C_{60} with a twofold excess of anthracene in carbon disulfide (20 °C, 28 days) gave rise to a mixture of five bis-adducts in a total yield of 45%, the *anti*-bis-adduct being the minor product (the yield was 1.6%).[252] Similar results were obtained with the use of other solvents.[387]

Regioselectivity of bis- and polycycloaddition can also be controlled by the use of templates,[214,352,360,385,388] which tether two diene fragments thus imposing geometric restrictions on the approach of the diene to monofunctionalized fullerene. For example, the α,α´-dibromo-*o*-xylylene fragments, which were tethered by the hydrocarbon chain containing from two to five atoms, were used for this purpose.[252] It was demonstrated that in the case of short chains (n = 2 and 3), *o*-quinodimethanes generated under the action of the KI—18-crown-6 system added to fullerene upon heating to give only two isomeric bis-adducts. An increase in the length of the chain to n = 4 leads to the formation of a complex mixture of bis-adducts. However, in the case of n = 5, the only bis-adduct was isolated in 30% yield (NMR analysis of the mixture revealed the presence of a number of by-products, but their total yield was at most 3%). The subsequent removal of the hydrocarbon chain from the isomeric adducts afforded fullerene derivatives, which can be functionalized by modification of the phenol fragments (Scheme 172).

In the case of n = 5, high regioselectivity of bis-cycloaddition was retained upon the replacement of the central carbon atom by the oxygen atom although the latter process afforded the *cis*-2 isomer along with the major product (*e* isomer).[389] The same two adducts (but in higher yields) were obtained by the reaction of bis(quinodimethane) based on dibenzo-18-crown-6 (Scheme 173).

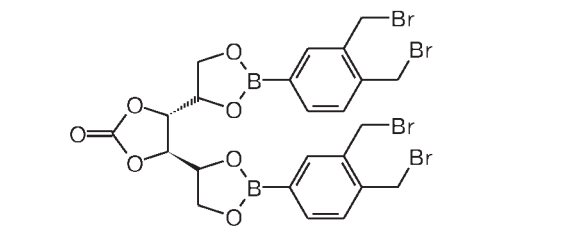
Scheme 172



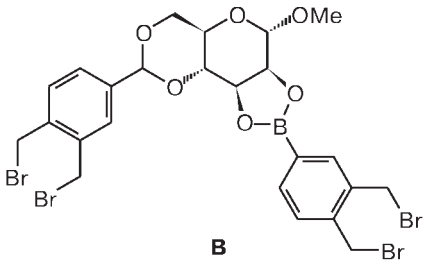
Reagents and conditions: *i*. KI/18-crown-6, toluene, Δ; *ii*. BBr_3.

Boric esters of saccharides **A**—**D** were also used as template agents.[390]

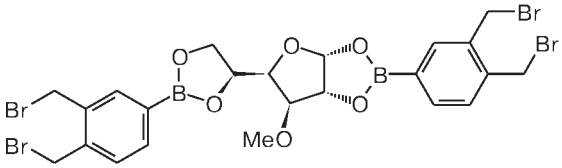
In the cited study, the *in situ* generation of bis(*o*-quinodimethanes) was also described. This synthesis was car-



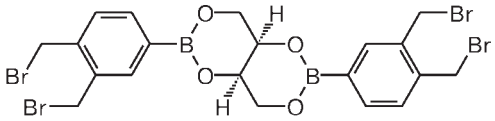
A



B



C



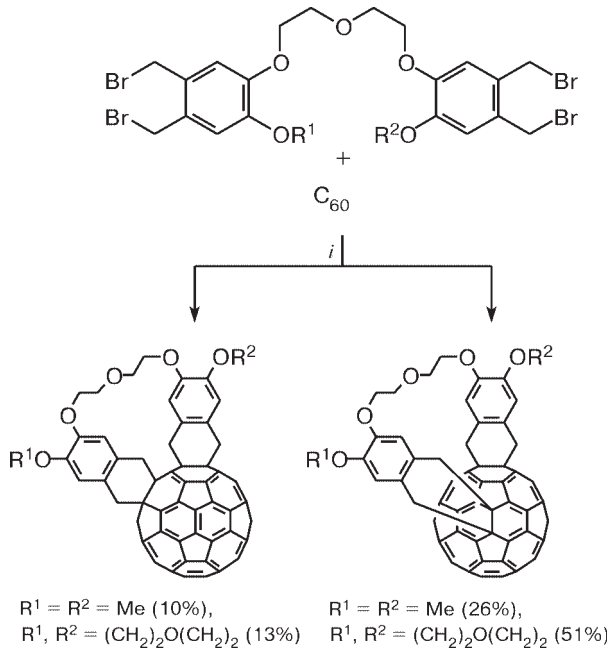
D

ried out by refluxing di(bromomethyl)arenes with potassium iodide in toluene in the presence of 18-crown-6 However, mixtures of seven—eight isomers were obtained in all cases. The highest selectivity was achieved with the use of a glucofuranose derivative. In the latter case, the major bis-adduct was obtained in 72% yield, which allowed its isolation and identification as the *trans*-4 adduct (Scheme 174).

8.2. Polycycloadducts

Seven out of 46 possible positional isomers of tris-[di(ethoxycarbonyl)methano][60]fullerene were isolated and their electrochemical properties were studied.[391]

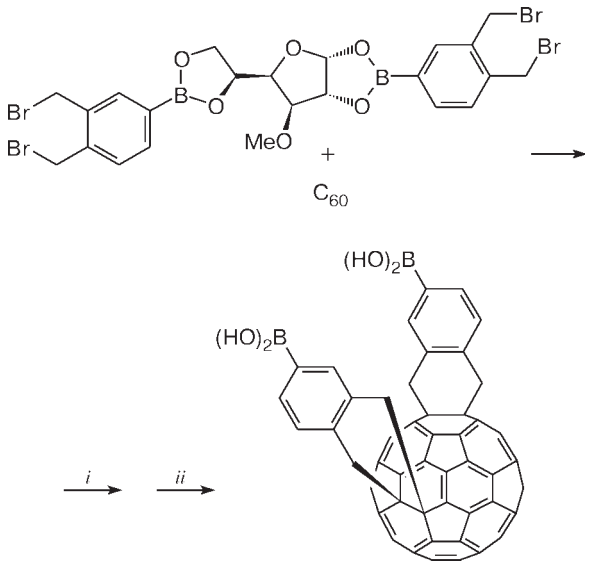
Scheme 173



i. KI/18-crown-6, toluene, Δ.

Among the remaining adducts, 36 isomers contain addends in the unfavorable *cis* orientation.[363] The tris-adducts that were isolated were characterized exclusively by the *e*-, *trans*-4-, *trans*-3, and *trans*-2 mutual arrangement of the addends because they were prepared from the corresponding bis-adducts with the same positional arrangement. Cyclopropanation of *e*-$C_{62}(CO_2Et)_4$ and *trans*-2-$C_{62}(CO_2Et)_4$ afforded the *e,e,e*- and *e*,*trans*-3,*trans*-2 isomers, respectively, as the major products with rather high regioselectivity. Cyclopropanation of *trans*-3-$C_{62}(CO_2Et)_4$ proceeded virtually statistically with the *trans*-3,*trans*-3,*trans*-3 tris-adduct slightly predominating. The intermediate situation was observed in the cyclopropanation reaction of *trans*-4-$C_{62}(CO_2Et)_4$, which afforded four out of five possible isomers including

Scheme 174



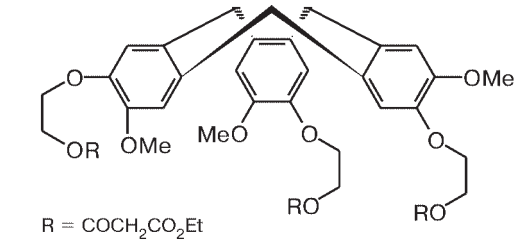
Reagents and conditions: *i*. KI/18-crown-6, toluene, Δ; *ii*. HCl, THF.

at least one *trans*-4 position in non-statistical amounts. Quantum-chemical calculations of some starting bis-adducts demonstrated that the site of the predominant attack is determined by the coefficients of the frontier orbitals.

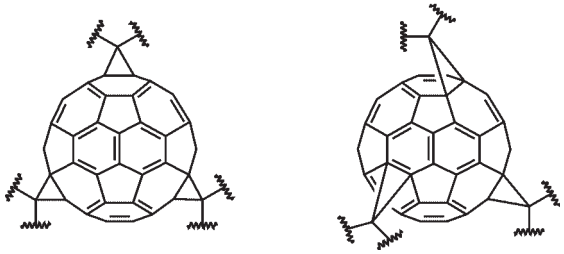
Isomeric tris-adducts	Yield* (%)			
	e	*trans*-4	*trans*-3	*trans*-2
e,*e*,*e*	35.5	—	—	—
trans-3,*trans*-3,*trans*-3	—	—	28.5	—
e,*trans*-3,*trans*-2	47.8	—	27.5	86.5
trans-4,*trans*-3,*trans*-3	—	26.6	19.7	—
e,*trans*-4,*trans*-3	16.9	44.2	—	—
trans-4,*trans*-4,*trans*-2	—	10.3	—	—
e,*trans*-4,*trans*-2	—	18.9	—	13.5

* With respect to the starting bis-adduct.

As in the case of bis-adducts, the problem of regioselectivity of tris-addition is resolved with the use of directing tethers. Thus the one-step Bingel reaction with the use of the C_3-symmetrical tris-malonate derivative of cyclotriveratrylene made it possible to obtain[392] exclusively the C_3-symmetrical *e,e,e*- and D_3-symmetrical *trans*-3,*trans*-3,*trans*-3 structures in a ratio of 45 : 55.



R = $COCH_2CO_2Et$



(±) *trans*-3,*trans*-3,*trans*-3 (11%)

(±) *e*,*e*,*e* (9%)

In the synthesis of tetrakis-adducts, the regioselectivity of the addition processes can be controlled not only with the use of directing spacers but also employing the above-described template procedure consisting in the temporary insertion of easily removable directing addends. For example, triple Bingel cyclopropanation of tris-adduct **84** directed at the equatorial zone afforded intermediate hexakis-adduct **85**. The elegant removal of two cyclohexadiene rings from compound **85** by the successive Diels—Alder reaction with acetylenedicarboxylic ester and the retro-Diels—Alder reaction afforded D_{2h}-symmetrical tetrakis-adduct **86** [393] (Scheme 175).

The use of thermally labile anthracene template agents for these purposes is based on the fact that anthracene [2+4]-bis-adduct **87** contains two anthracene addends at the opposite sides ("poles") of the fullerene sphere. Hence, it was expected that these bulky addends would control the subsequent polycyclopropanation reactions by directing them at the equatorial position of the molecule to form mixed symmetrical hexakis-adduct **88**.[394] Actually, treatment of a suspension of compound **87** in dichloromethane with an excess of diethyl bromomalonate in the presence of DBU at room temperature for 2 days gave rise to hexakis-adduct **88** in 95% yield. Heating of solid adduct **88** (in the absence of oxygen) at 195 °C for 5 min afforded anthracene-free D_{2h}-symmetrical tetrakis-adduct **86** (88%) (Scheme 176).

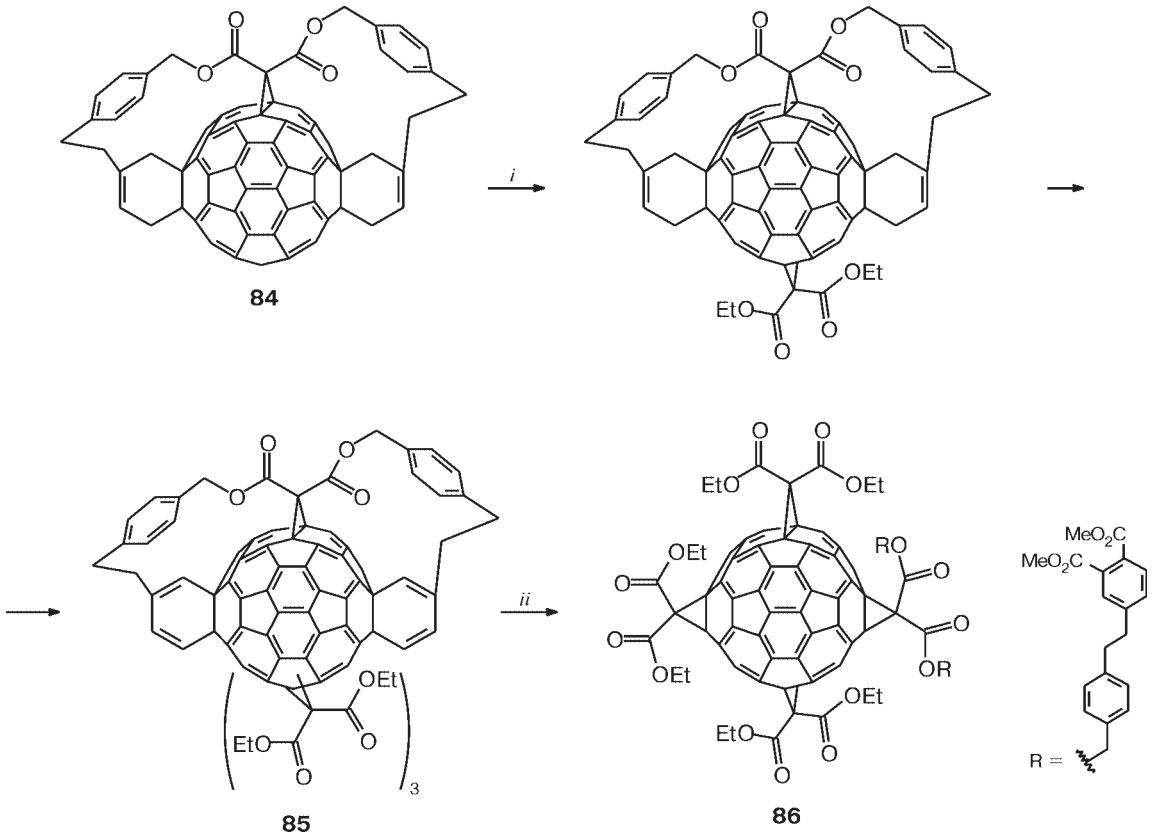
The monoadduct with anthracene, unlike the bis-adduct, is not sufficiently efficient for regioselective attack. Cyclopropanation of the adduct of fullerene with 2,6-dimethoxyanthracene under the action of ethyl bromomalonate followed by the retro-Diels—Alder reaction afforded a mixture of seven bis-adducts,[208] which is virtually identical with that obtained by direct cyclopropanation of fullerene.[351]

Thermal lability of the 9,10-dimethoxyanthracene (DMOA)[395] and 1,9-dimethylanthracene[396] addends was exploited in the synthesis of the hexakis-adduct $C_{66}(CO_2Et)_{12}$ by the Bingel reaction. The Diels—Alder reaction with a tenfold excess of DMOA was reversible even at room temperature and produced predominantly the $C_{60}(DMOA)_2$ and $C_{60}(DMOA)_3$ adducts as a mixture of regioisomers.[395] The thermodynamic control over the process is of additional importance. For this reason, the C_3-symmetrical *e,e,e*-isomer with the incomplete octahedral structure prevailed among various regioisomers of $C_{60}(DMOA)_3$ (according to the UV spectra). In this isomer, the intact unsaturated octahedral bonds are substantially activated with respect to the subsequent addition, for example, to addends, which are irreversibly bound. The DMOA addends can be successively or simultaneously replaced by other addends. Thus, irreversible cyclopropanation of a mixture of the [2+4]-adducts of DMOA with C_{60} under the action of diethyl bromomalonate in the presence of DBU afforded hexakis-adduct $C_{66}(CO_2Et)_{12}$ **89** in 48% yield (Scheme 177).

In the case of fullerenotriazoline **90**, an analogous procedure of the simultaneous use of DMOA and diethyl bromomalonate initially afforded mixed hexakis-adduct **91** from which the pentakis-adduct $C_{65}(CO_2Et)_{10}$ (**92**) was obtained by successive elimination of N_2 and decyclization of the imine ring[395] (Scheme 178).

Direct cyclopropanation of C_{60} with mesomorphic double cyanobiphenyl malonates gave rise to the hexakis-adduct in small yield (9%) along with the monoadduct

Scheme 175



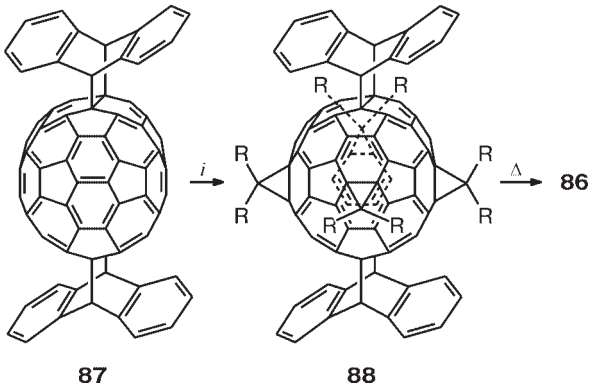
84 85 86

Reagents and conditions: *i*. 3 equiv. of $BrCH(CO_2Et)_2$; *ii*. $MeO_2CC{\equiv}CCO_2Me$, $PhCH_3$, reflux.

(43%). The former compound possesses liquid-crystalline properties[397] and is analogous to **89** with the difference that $R = CO_2(CH_2)_{10}OC_6H_4Ph$-4.

The Diels—Alder reaction finds use not only for insertion of templates into the C_{60} molecule but also for the preparation of polycycloadducts. For example, the reaction of fullerene with 9,10-dimethylanthracene (DMA) at room temperature afforded a mixture of the $C_{60}(DMA)_x$ adducts.[206] Thorough analysis of a mixture prepared by heating fullerene C_{60} with 15 equiv. of DMA revealed the presence of the monoadduct, 6 bis-adducts, 11 tris-adducts, and 10 tetrakis-adducts.[223] Seven bis-adducts were found in the mixture obtained by the reaction of fullerene

Scheme 176

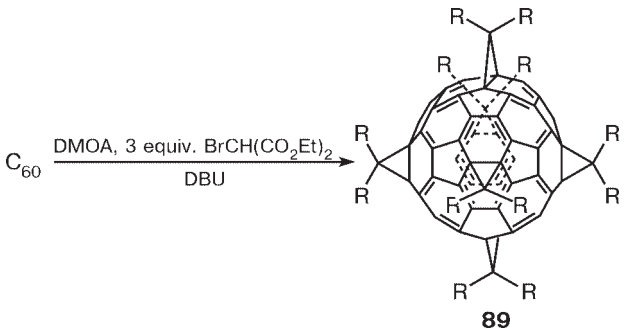


87 88

$R = CO_2Et$

i. 3 equiv. of $BrCH(CO_2Et)_2$, DBU.

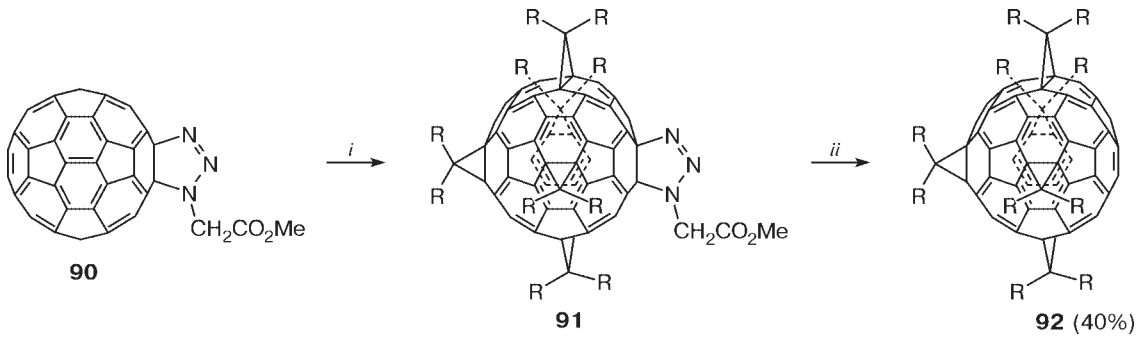
Scheme 177



89

$R = CO_2Et$

Scheme 178

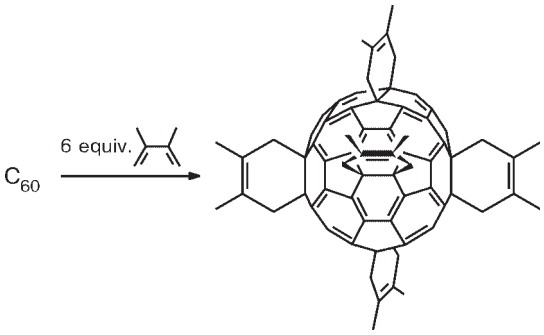


Reagents and conditions: *i.* DMOA, 3 equiv. of $BrCH(CO_2Et)_2$, DBU; *ii.* $PhCH_3$, reflux.

with 2.5 equiv. of 4,5-dimethoxy-*o*-quinodimethane generated *in situ* from the bis(bromomethyl) derivative.[398] The cycloaddition reactions of dienes generated from 2,3-bis(bromomethyl)tetrathiafulvalenes bearing various alkylthio substituents afforded eight bis-adducts and a complex mixture of tris- and tetrakis-adducts along with the monoadduct.[330] The absence of selectivity in the polycycloaddition of dienes to fullerene was explained based on the results of quantum-chemical calculations for the Diels—Alder reaction of butadiene with fullerene.[399] The authors of the cited study demonstrated that the competitive reactions of formation of different isomers of the bis-adduct are charaterized by virtually identical enthalphies and the corresponding energy barriers. It should be noted that the energy barries are only little different from the corresponding values for the formation of tris-, tetrakis-, pentakis-, and hexakis-adducts.

The use of a large excess of diene made it possible to prevent the formation of a complex mixture of mono-, di-, and polyadducts to give predominantly the symmetrical hexakis-adduct[400] (Scheme 179).

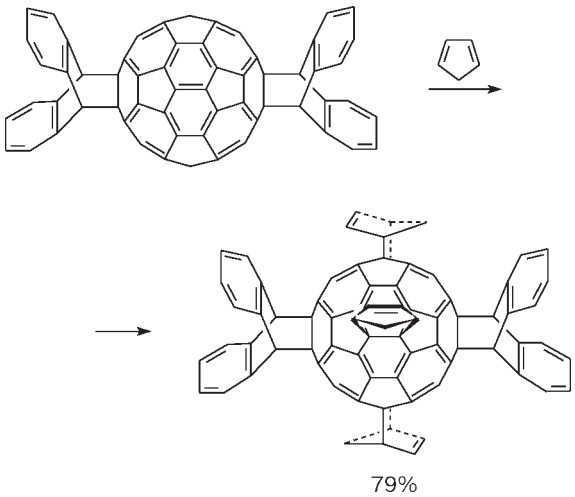
Scheme 179



At the same time, the reaction with an excess of 2,3-dimethylbutadiene was accompanied[185] by the formation of the corresponding symmetrical tetrakis-adduct.

Under the action of an excess of cyclopentadiene, the *anti*-bis-anthracene adduct of fullerene produced the pseudooctahedral adduct containing two anthracene and four cyclopentadiene fragments[394] (Scheme 180).

Scheme 180



The possibility of the formation of polyadducts depends not only on the ratio of the reagents but also on the reactivity of the diene fragment. It was demonstrated that 2,5-dimethylthiophene *S*-oxide prepared by *in situ* oxidation of 2,5-dimethylthiophene gave only the monoadduct even in the presence of a 64-fold excess relative to fullerene, whereas the corresponding *S*,*S*-dioxide under analogous conditions produced the tetrakis-adduct.[401] Some other processes, for example, the reaction of fullerene with 10 equiv. of 2,3-dimethylene-7-oxanorbornane, did not yield polyadducts either.[212]

To find out the extent to which diazomethane adds to the highly functionalized carbon sphere characterized by substantially reduced electrophilicity and to elucidate whether the product of nitrogen elimination from intermediate pyrazolines is analogous to that observed in the reaction of fullerene, the authors of the cited[402] study used C_{2v}-symmetrical pentakis-adducts, which were syn-

thesized by double cyclopropanation of tris-adduct **84**, as the starting compound. It appeared that the reaction with diazomethane proceeded with high regioselectivity to form new hexakis- and octakis-adducts. The authors believed that thermal elimination of nitrogen from intermediate pyrazolines is controlled by orbital symmetry.

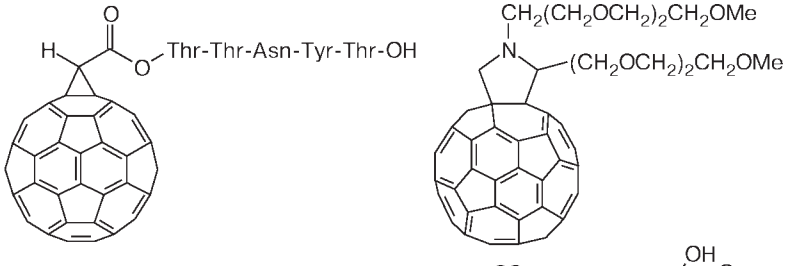
Multiple [2+3]-cycloaddition of ylide, which was generated from 2,2-dimethylglycine and acetone, to C_{60} gave rise to T_h- and D_3-symmetrical hexakis-adducts. These compounds exhibit unusually bright yellow-blue fluorescence, which has not been observed previously for other polyadducts.[403]

Theoretical calculations (AM1) demonstrated that the observed regioselectivity of polycyclopropanation of C_{60} is determined by orbital-controlled processes.[404] Besides, the authors of the cited study proposed the general algorithm for the notation of the 6,6- and 6,5-bonds in fullerene polyadducts in addition to the commonly accepted nomenclature.[351] This algorithm allows the unambiguous description of the mutual arrangement of the addends and the absolute configuration of a particular fullerene derivative.

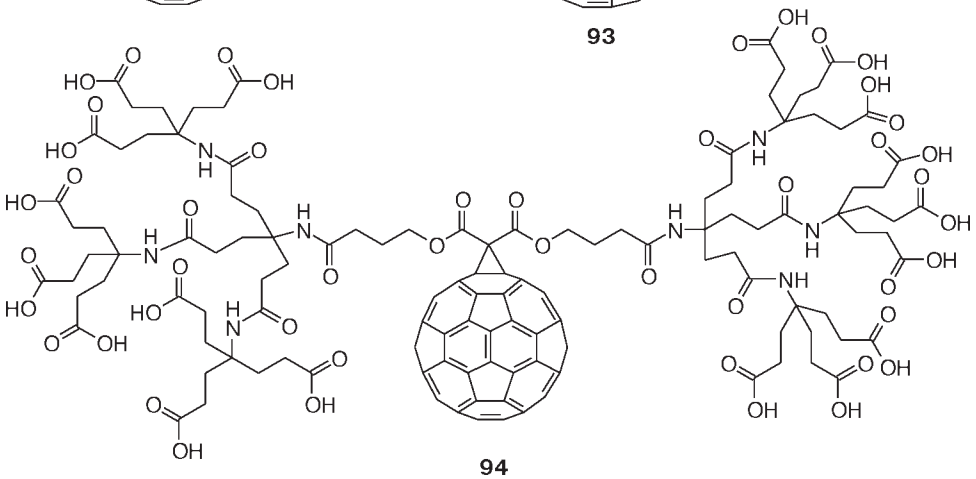
9. Biological activity of fullerene cycloadducts

Since, as mentioned at the beginning of the review, primary recent attention has been given to the target-directed construction of [60]fullerene derivatives possessing useful properties, at the conclusion of the review particular emphasis should be placed on biological activities of these compounds, which is presently the vital problem. The major trends in these investigations can be demonstrated with several examples. Apparently, the size, hydrophobicity, the three-dimensionality, and the electronic properties of fullerenes are very attractive for the medicinal chemistry.[405] For example, it can readily be imagined that the spheroid surface of fullerene can potentially be coordinated at the hydrophobic regions of enzymes or cells thus providing the possibility of their biological use in different fields. The biological properties of fullerene derivatives were surveyed in a number of reviews.[405—414]

Biological investigations of fullerene derivatives are difficult primarily because of hydrophobicity of fullerene. One possible way of overcoming this difficulty is to carry out a chemical modification of the sphere by inserting solubilizing fragments. This approach has received general acceptance in the target-directed synthesis of potent biologically active fullerene cycloadducts. Several examples of such water-soluble fullerene derivatives can be given. One of such cycloadducts, *viz.*, compound **93**, can be dissolved in the concentration as high as $1.5 \cdot 10^{-5}$ mol L^{-1} in a 9 : 1 H_2O—DMSO mixture. The record-breaking solubility was achieved for dendrimer **94** (its solubility in water is 34 mg mL^{-1} at pH 7.4 and 254 mg mL^{-1} at pH 10).[406] Hence, the insertion of hydrophilic substituents into the C_{60} sphere makes it possible to achieve sufficiently high solubility in water. It should be noted that all these and analogous fullerene derivatives can be readily prepared according to procedures for functionalization considered in the present review. Thus, water-soluble dendrimer **94** was synthesized by the Bingel



93

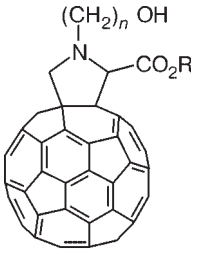


94

reaction.[6] The cited study was based on the assumption that the unique ability of [60]fullerene derivatives to capture radicals is an ideal prerequisite for the therapeutic treatment of neurodegenerative diseases.

From the viewpoint of biological activity, fullerene-containing amino acids and peptides are also of great interest. As an example we refer to optically active fullerenoproline,[130] which is apparently the largest non-natural amino acid, and the derived di- and tripeptides (both through amino and carboxylic groups) (see Ref.[415]). This interest stems from investigations of the effect of the fullerene core on the unique ability of proline derivatives to influence the polypeptide folding resulting from the conformational features of these derivatives.[403]

Examinations of interactions between some enzymes and fullerenoprolines[416] are equally interesting. These studies potentially have several aspects. First, fullerene derivatives exhibit biological activity, which is, in some cases, associated with inhibition of enzymes.[412] Second, enzymatic reactions involving bulky substrates can be very unusual. Fullerenoproline derivatives **95a—c** prepared by the Prato reaction were used as such substrates.

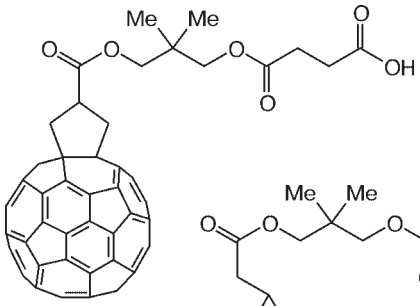


95a—c

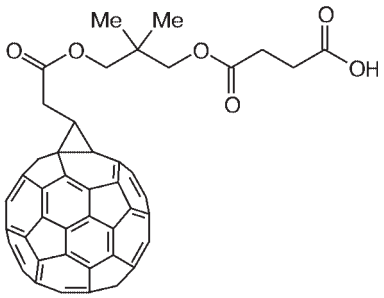
a: R = Et, *n* = 3; **b:** R = Bu^t, *n* = 2; **c:** R = Bu^t, *n* = 3

Compounds **95a—c** were chosen as convenient models for revealing the effects of the distance from the fullerene sphere to the reaction center and the steric hindrances caused by the proline ester group. Enzymatic transesterification of **95** with alcohols was successfully carried out only in the case of 2,2,2-trifluoroethyl palmitate and only with the use of lipase B from *Candida Antarctica* and lipoprotein lipase from *Pseudomonas species*. The former enzyme proved to be more efficient as a catalyst of esterification of fullerene derivatives. It appeared that both lipases respond to steric features of substrates in much the same way. Thus, the bulky ester groups substantially slow down enzymatic reactions, whereas the length of the alkyl chain at the nitrogen atom exerts only a slight effect on the reaction. Both lipases exhibit moderate enantioselectivity resulting in the cleavage of the C_α-chiral center of the proline ring in substrates **95a,b**, which is also of importance for revealing the characteristic features of enzymatic reactions depending on the structure of the substrate.

The fact that cycloaddition products give a weak absorption band at 700 nm allows their application in the photodynamic therapy owing to more efficient penetration of longer-wavelength light through tissues.[38] Photoexcited fullerene derivatives can either generate singlet oxygen that cleaves DNA or directly oxidize biomolecules by the mechanism of electron transfer. Apparently, it is these effects that are responsible for the ability of C_{60} derivatives to exert cytotoxic action.[393] For example, *in vitro* assays in tumor cells HeLa S3 using fullerenocyclopentane **96** demonstrated that cytotoxic activity is manifested only under irradiation.[394]



96



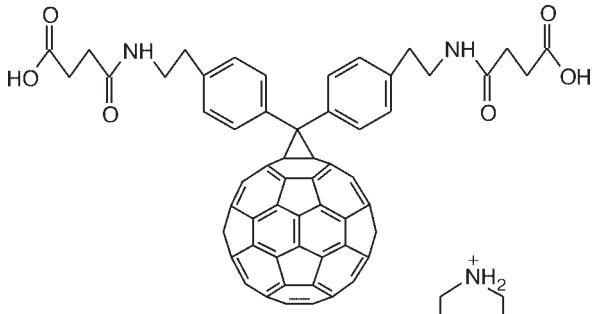
97

Another example of antitumor activity was observed upon local irradiation of mice innoculated with fibrous tumor, which were treated with functionalized [60]fullerene derivatives.[417] In these experiments, not only reduction of the tumor mass but also tumor necrosis without skin injury were observed. It was noted that C_{60} derivatives are accumulated in a tumor due to excellent vascular permeability and relative immaturity of the lymphatic system of tumor tissues rather than because of specific tropism.

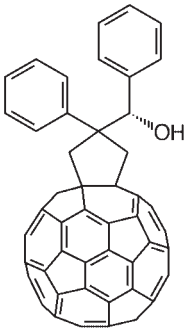
Fullerene derivatives **96** and **97** show inhibiting activity with respect to cysteine proteases (papain and cathepsin) and serine proteases (trypsin, plasmin, and thrombin).[406,418] The mechanism of inhibition remains unknown, but it is assumed that hydrophobicity and electrophilicity of the fullerene spheroid are of great importance for inhibition.

It is these properties that are apparently responsible for anti-HIV activity of fullerene cycloadducts. The active side of HIV protease is a quasi-spherical hydrophobic cavity with the diameter of ~10 Å. Two amino acid residues (Asp25 and Asp125) located on its surface catalyze hydrolysis of the substrate and, hence, inhibition of hydrolytic activity can lead to shielding of the protein layer and, as a consequence, to termination of internal virus replica-

tive cycle.[419] Based on the results of molecular modeling, it was established that the fullerene spheroid is coordinated predominantly at the hydrophobic side of this enzyme,[412] *i.e.*, inhibition of HIV protease would be expected in the case of sufficiently strong interactions. Actually, this inhibition was observed for a water-soluble compound **97**.[420] The basic idea of constructing the most active fullerene inhibitors of HIV protease consists in choosing structures, which sterically fit the channels in the hydrophobic cavity of the enzyme.



98



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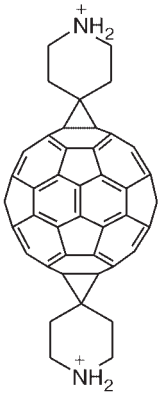


100

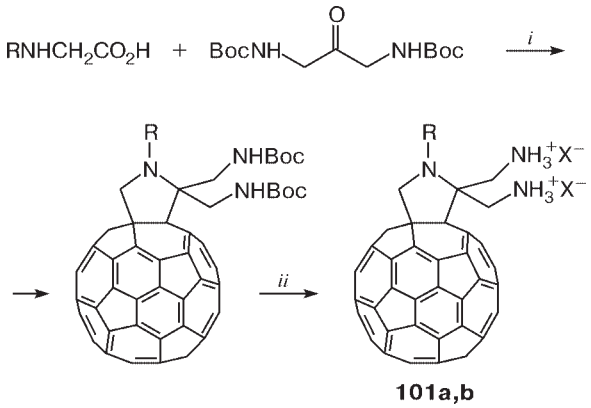
Actually, compound **98** cannot occupy these channels for steric reasons, whereas calculations carried out for compounds **99** and **100** demonstrated that these cycloadducts can occupy channels in the hydrophobic cavity and the binding constant for compound **99** is 5 times as large as that for compound **98**.[421]

In addition, Coulomb interactions and/or hydrogen bonds must also lead to an increase in the constant of binding of fullerene derivatives with the Asp residues of HIV protease. Bis-ammonium derivatives of fullerenopyrrolidine **101a,b** prepared[422] by the Prato reaction (Scheme 181) satisfy these requirements.

To evaluate the ability of these compounds to bind with the cavity of HIV protease, molecular modeling was carried out with the use of the Discover program (Biosym/MSI), which revealed this ability for substrate **101a**.

Many neurodegenerative diseases are caused by excessive production of NO radicals resulting from hyperexcitation of glutamic acid receptors. Hence, compounds serving as free-radical scavengers can prevent neuron death.[407] Such activity of C_{60} derivatives is known. Actually, in the *in vitro* experiments two regioisomeric triscyclopropane adducts **102** and **103**, which are readily soluble in water and serve as excellent free-radical scavengers, showed a dose-dependent decrease in the degree of neuron death, and compound **102** proved to be more active.[422]

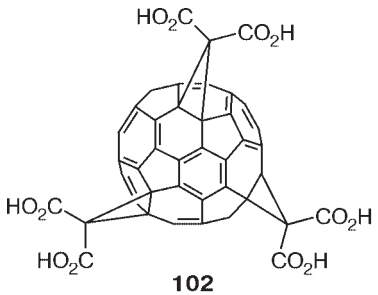
Scheme 181



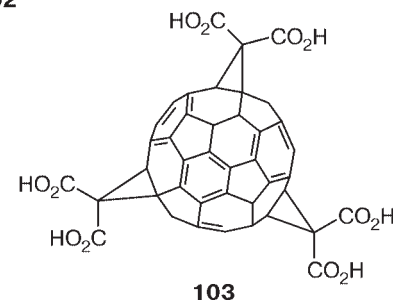
101a,b

R = Me (**a**), $CH_2CH_2OCH_2CH_2OCH_2CH_2OMe$ (**b**); X = Cl, CF_3CO_2

Reagents and conditions: *i*. C_{60}, toluene, Δ; *ii*. HX, CH_2Cl_2.



102



103

According to the preliminary data, water-soluble cycloadduct **98** is active with respect to different microorganisms.[423] This compound kills various bacteria and fungi, which are often resistant to other antibacterial agents, in slightly modified agar-diffusion test.

In conclusion, is should be noted that [60]fullerene derivatives show promise not only due to the above-mentioned various biological properties but also owing to their rather low toxicity. Thus, preliminary toxicological inves-

tigations demonstrated that C_{60} derivatives are non-cancerogenic when applied to skin, and studies of acute and subacute toxicity gave negative results. All the aforesaid clearly show that the further development in the field of medicinal chemistry of fullerene derivatives has considerable promise.

10. Prospects of the development of the chemistry and practical applications of fullerene cycloadducts

Based on analysis of the data surveyed in the present review, predictions can be made concerning the further development of the chemistry and practical applications of fullerene derivatives. The further progress in the chemistry of fullerene cycloadducts may be associated with the following major lines of their application: 1) unusual electrochemical properties;[324] 2) broad variation in photophysical and photochemical properties of substituted fullerenes;[324] 3) potential pharmacological properties; 4) ferromagnetic properties;[425] 5) superconducting properties;[426] 6) nonlinear optics (see Refs. 344, 427, and 428); 7) the ability to form Langmuir—Blodgett films; 8) synthesis of fullerene-containing polymers possessing one of the above-mentioned properties.

Interest in the photophysical properties of fullerene derivatives arises primarily from the fact that fullerene—spacer—donor systems are rather readily excited giving rise to charge-separated states. As discussed above, the lifetime of this excited state may vary over a wide range depending on the type of the functional group bound to fullerene as well as on the length and the type of the spacer between fullerene and the functional group. The existence of long-lived charge-separated excited states will allow the use of the corresponding cycloadducts for the conversion of the solar light energy to the chemical energy and other kinds of "recoverable" energies.[86,429—431] To the contrary, substrates with short-lived excited states can be used as highly sensitive detectors in systems for rapid data processing, *etc*. In addition, the photodynamical properties of fullerene-based cycloadducts allow their applications as photodiods, reagents for photochemical cells, optical sensors, fluorescence agents, and materials possessing photoswitching, including photochromic and electrooptical, properties. In the latter case, both photodynamic and unusual electrochemical properties of fullerene derivatives are of importance.[432,433]

Among other possible applications of fullerene derivatives, mention may be made of the application of fullerene-containing polymers as materials possessing photorefractive properties, which are used for obtaining three-dimensional holographic images.[434] The characteristic properties of these materials are charge photogeneration, transfer and spatial separation of charges, and formation of systems with spatial modulation of the refractivity. At least the first three properties are readily realized with the use of many donor—spacer—fullerene systems. The last-mentioned property is manifested by nonlinear optical materials. Some fullerene-based cycloadducts also exhibit these properties. It should be noted that qualitatively similar porphyrin—spacer—acceptor systems (with polyimide fragments as acceptors) have already been used for this purpose.[435]

Another promising field is the application of fullerene derivatives containing electron-donating functional groups such that they undergo fragmentation at the C—X bond after the photoinduced electron transfer to fullerene (for example, amino alcohols). This photoinduced fragmentation attendant on the intermolecular electron transfer is well known (see, for example, Ref. 436). This approach has recently been used for enhancing photosensitivie efficiency of color films with increased light sensitivity due to a sharp increase in the quantum yield of the overall process.

Thin films based on fullerene cycloadducts have potential application relying on their optical, ferromagnetic, and superconducting properties.[437—440] The main advantage of Langmuir—Blodgett films is the possibility for the preparation of materials possessing particular properties on the nanosized level. High tendency of fullerene derivatives to the formation of such films gives promise that their cycloadducts will find use in the nanochemistry, which is the rapidly developing field.

The potential use of fullerene cycloadducts in medicine relies on two principal properties of the fullerene core, *viz*., on high lipophilicity, which allows fullerene derivatives to penetrate through cell membranes, and on their ability to generate DNA-cleaving singlet oxygen in high quantum yield. These properties endow cycloaddition products of fullerene with cytotoxic, anti-HIV, and other useful activities and allow their use as agents for photodynamic cancer therapy.[58,84,115,308,405—407,409—414,418,420,421,441—446]

Besides, chiral fullerene cycloadducts show promise as catalysts of the asymmetric synthesis. Considerable steric requirements of fullerene may ensure high efficiency of such chiral catalysts.

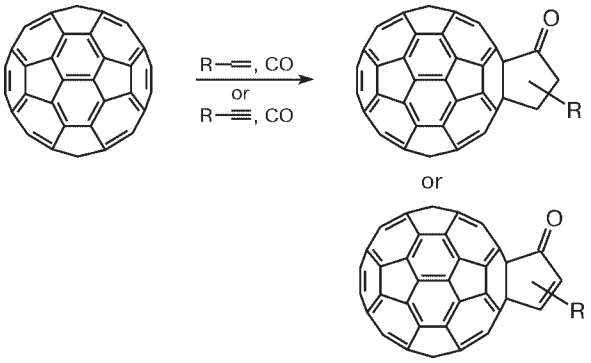
Due to the liquid-crystalline properties, fullerene derivatives also have a great potential from the technical standpoint.[397,447—449]

Finally, polyadducts provide an excellent basis for the preparation of various dendrimers.[106,362,450—452]

As mentioned above, the extension of the scope of cycloaddition reactions by employing new addends and developing new cycloaddition reactions is of obvious interest from the viewpoint of synthetic investigations. Among other cycloaddition reactions, of interest are the application of fullerene as the olefin component in the Pauson—Khand reaction, which was not described in the literature (Scheme 182) and also its use in various "domino" processes, such as [2+4]/[2+3]-cycloaddition of nitroalkenes (see, for example, Ref. 453), *etc*. The de-

velopment of a procedure for cyclotrimerization of fullerene with alkynes and alkenes containing electron-withdrawing substituents in the presence of tertiary phosphines (an analog of the Paterno—Büchi reaction) (see Ref. 294) is also of interest.

Scheme 182



To summarize, from the aforesaid it is believed the chemistry of fullerene derivatives will be fruitfully developed for many years to come.

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