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Accounts

Biscycloaddition to [60]Fullerene: Regioselectivity and Its Control with Templates

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Compared to [60]fullerene monoadducts, there have been far fewer examples of the investigation of bisadducts, mainly due to the difficulties in their isolation and characterization. Unless appropriate templates are employed, bisadditions generally proceed with low regioselectivity, resulting in the formation of complex regioisomeric mixtures. This account deals with the regioselectivity in typical bisadditions in the absence of templates and the spectroscopic features available for the characterization of the bisadducts produced. The observed regioselectivity can be reasonably explained by a combination of the steric reasons and the coefficients of frontier orbitals in the corresponding monoadducts. Although it depends on the reactive species whether HOMO or LUMO is involved, *e* isomer is always preferable. In order to accomplish regioselective synthesis of bisadducts, several research groups have developed a synthetic methodology by using tethers as covalent templates. This account describes the regioselectivity in bisadditions accomplished by templating tethers, mainly focusing on Diels–Alder reactions.

Over the past decade, the reactivity of [60]fullerene has been extensively investigated, and a variety of monoadducts have become available.[1] Most addends attack [6,6] junctions (bonds between two six-membered rings) of [60]fullerene, not [5,6] junctions (bonds between a six-membered ring and a five-membered ring), to give monoadducts as a single isomer. Although two π-electrons are lost out of 60 and the symmetry of molecule is reduced as a result of addition to a [6,6] junction, the original π-electron system of [60]fullerene is mostly preserved.

In contrast with monoadducts, there have been only limited examples of the preparation of multiple adducts, because the number of possible regioisomers drastically increases with the number of additions. Practically, most multiple addition reactions in solution afford several regioisomers, the separation of which usually requires highly sophisticated chromatographic techniques. In the bisaddition, trisaddition, and tetrakisaddition of symmetrical addends occurring exclusively at [6,6] junctions, 8, 46, and 262 regioisomers are possible in principle, respectively. The eight patterns of bisaddition, first named as *trans*-1, *trans*-2, *trans*-3, *trans*-4, *e*, *cis*-3, *cis*-2, and *cis*-1 by Hirsch et al.[2] depending on the relative positional relationships, are illustrated in Fig. 1. For the nomenclature of fullerenes and their derivatives, following the preliminary survey published in 1997,[3a] IUPAC recommendations were presented in 2002, although the latter was limited to [60]fullerene and [70]fullerene and their derivatives.[3b] Figure 1 also denotes the descriptions based on IUPAC recommendations. These bisadditions bring about further disconnection of the conjugated system in [60]fullerene, and produce novel π-electron systems which differ from those of [60]fullerene itself and its monoadducts, depending on addition pattern. Furthermore, *trans*-2, *trans*-3, and *cis*-3 regioisomers with a C_2-symmetry have a chirality on the π-system of [60]fullerene chromophore derived from their addition pattern, even though two identical, achiral addends are introduced. Thus, several research groups have prepared various bisadduct regioisomers and have disclosed their electronic, electrochemical, photophysical, and chiroptical properties independently. In addition, fullerene multiple adducts are also employed as the building blocks in the construction of supramolecular advanced materials.[4] Hence, to clarify the regioselectivity in bisadditions and to aim at preparing specific regioisomers are quite important subjects.

The systematic investigation on the regioselectivity in bisaddition was first carried out by Hirsch et al.[2] with using diethyl 2-bromomalonate and NaH at room temperature (Bingel reaction),[5] although there had been several earlier examples of the isolation and characterization of specific bisadducts. In this reaction, the regioselectivity was low, with the formation of seven regioisomers other than *cis*-1, although the second addition rather favors *e* and *trans*-3. Subsequently, the bisadditions involving other reactive species, such as nitrene,[6,7] carbene,[6,8] and azomethine ylide,[9,10] have been investigated, and some of them afforded all the possible eight isomers including *cis*-1.

In order to overcome such low regioselectivity, it is necessary to impose a steric restriction on the second addition step.

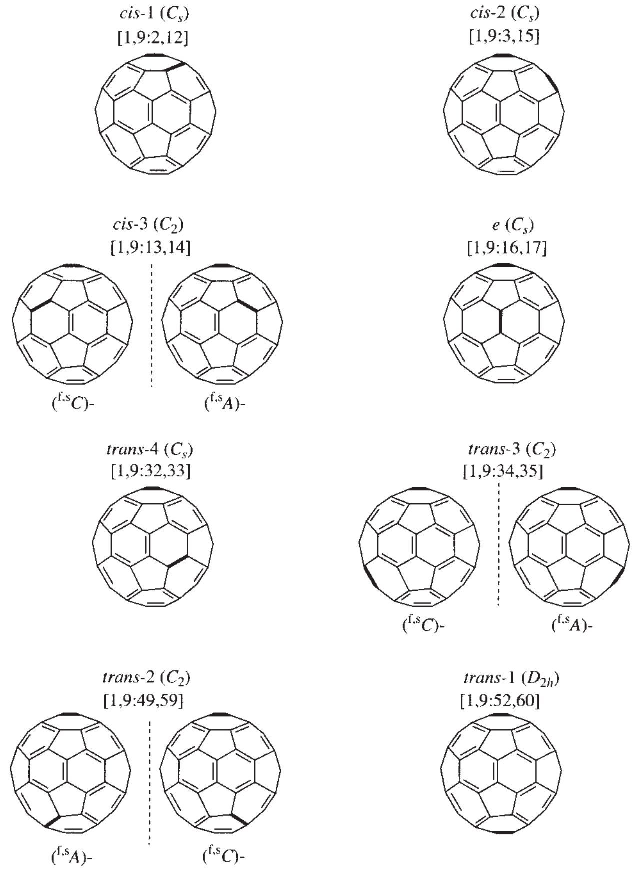


Fig. 1. Possible eight regioisomers of [60]fullerene bisadducts. Descriptions based on recent IUPAC recommendations (Ref. 3b) are also presented. The highest symmetries are given in parentheses.

Several research groups independently developed a synthetic methodology for controlling multiple additions efficiently, using tethers as covalent templates.[11,12] This method enabled the formation of bisadducts that would be difficult to obtain without suitable tethers. Diederich et al. achieved all possible bisaddition patterns except for *cis*-1 by utilizing Bingel reaction.

Since 1992, we have been interested in the functionalization of [60]fullerene, mainly by *o*-quinodimethanes and related species, and in the properties of resulting adducts,[13–17] because of the availability of their precursors and the high stability of the adducts.[18–20] In the course of study, we have been engaged in the chemistry of bisadducts and their applications. We have clarified the regioselectivity in bisaddition of *o*-quinodimethane and benzyne.[21,22] Furthermore, we have succeeded in the regioselective synthesis of [60]fullerene–*o*-quinodimethane bisadducts, mainly modified within one hemisphere of [60]fullerene, by connecting the two precursors with various linkages.

First, this account describes the regioselectivity in bisadditions without any templates. Although there have been multiple adducts formed by hydrogenation, radicals, or organometallic reagents,[23,24] this account only deals with biscycloadditions occurring mainly at two [6,6] junctions. The regioselectivity is also discussed from theoretical considerations. In addition, the spectroscopic features of bisadducts are presented. Second, this account focuses on the regioselective synthesis of bisadducts by taking advantage of covalent templates. The scope, limitation, and application of this methodology are described.

1. Biscycloaddition to [60]Fullerene without Templates

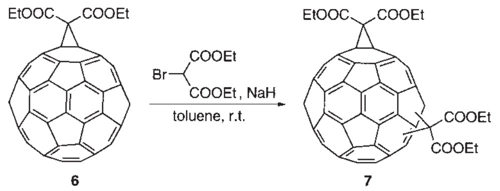
1.1 Examples of Biscycloadduct Regioisomers Isolated and Characterized. To the best of our knowledge, the first isolation and characterization of bisfunctionalized [60]fullerene was accomplished by Hawkins et al. using bisosmylation.[25] Five regioisomers (*trans*-1 to *trans*-4 and *e*) of $C_{60}[OsO_4L^*{}_2]_2$ **1** ($L^* =$ ligand; Chart 1) were separated by preparative HPLC and unambiguously identified based on the 2D NMR technique. While the isomer ratio of *trans*-1 to *trans*-4 and *e* was dependent on the ligands, *e* and *trans*-3 were major isomers and *trans*-1 was least formed.[25,26] The absence of *cis*-1–3 isomers can apparently be ascribed to the steric blocking of the osmyl group.

In the Diels–Alder reaction with anthracene, *trans*-1 bisadduct **2** (Chart 1) was first isolated from the reaction mixture by HPLC, followed by repeated reprecipitation; it was characterized by simple NMR spectroscopic data.[27] Later, five regioisomers other than *cis* isomers were isolated by column chromatography with a relative yield of *trans*-1:*trans*-2:*trans*-3:*trans*-4:*e* = 2:20:39:15:24.[28] Bisadduct **2** was efficiently and elegantly prepared in solid state; heating of the crystalline sample of [60]fullerene–anthracene monoadduct gave **2** and [60]fullerene in a 1:1 ratio by the intermolecular anthracene transfer.[29] The absence of other regioisomers indicates that this reaction is completely topochemically controlled.

In the oxidation of [60]fullerene by *m*-chloroperoxybenzoic acid (MCPBA) or other oxidation reagents, *cis*-1 isomer **3** (Chart 1) was most preferentially obtained among bisepoxy[60]fullerenes, $C_{60}O_2$, although other regioisomers were also detected on HPLC analysis.[30,31] In addition to the ^{13}C NMR spectral data, the X-ray crystallographic analysis of its iridium complex, $\mathbf{3}\cdot[IrCl(CO)(PPh_3)_2]$, undoubtedly proved its addition pattern.

The reactions of [60]fullerene with diamines such as *N*,*N*′-dimethylethylenediamine and piperazine afforded six and seven bisadduct isomers of **4** and **5** (Chart 1), respectively, along with monoadducts.[32–34] After HPLC separation, *trans*-3 and *e* of **4** were isolated and identified by several NMR experiments. For **5**, three regioisomers (*cis*-2, *trans*-3, and *trans*-2) were unambiguously characterized by X-ray crystallographic analysis.

In most of the bisadditions described above, the isolated and characterized regioisomers were only a portion of the generated ones, and the isomer distribution was not sufficiently revealed. Hirsch et al. have clarified the isomer distribution in various types of bisaddition. First, they examined the second addition of diethyl 2-bromomalonate to monoadduct **6** (Bingel reaction, Eq. 1).[2]



6 **7** (1)

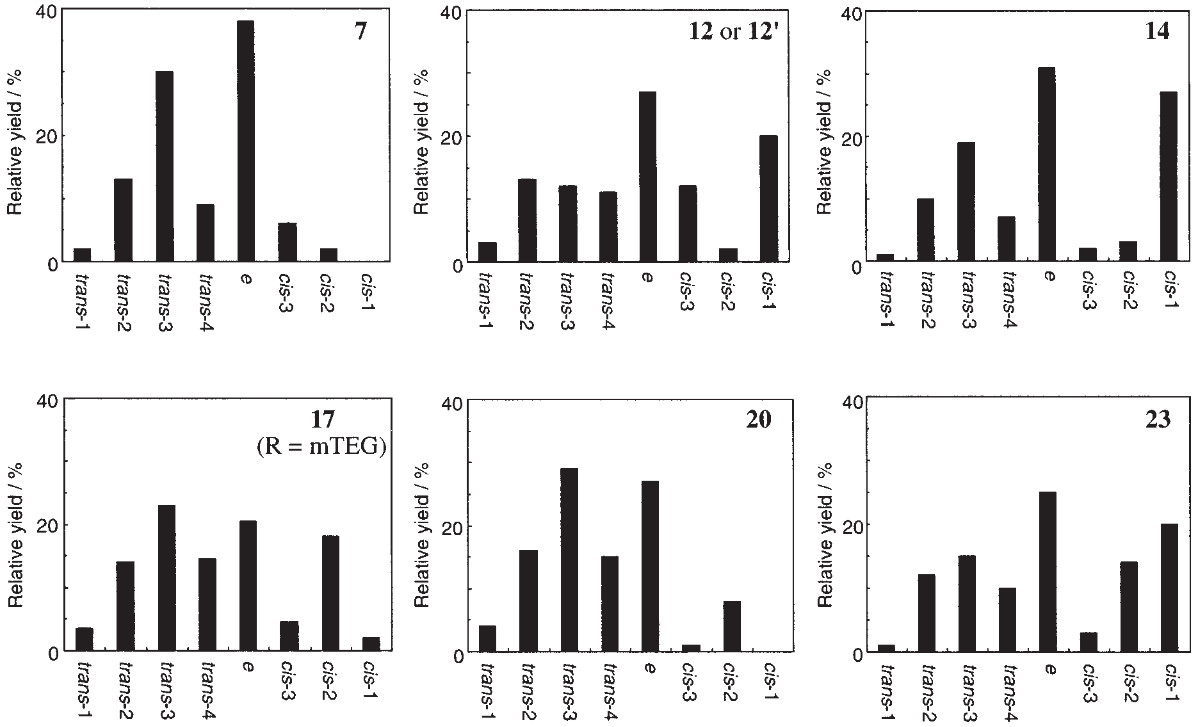
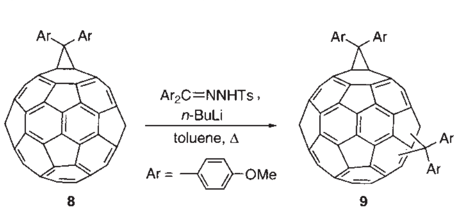


Fig. 2. Comparison of regioselectivity in the formation of bisadducts **7**, **12** (or **12′**), **14**, **17**, **20**, and **23**.

They successfully isolated seven regioisomers of **7** (not *cis*-1) by using HPLC and they thoroughly characterized them based on the NMR and UV-Vis spectroscopies and the elution order associated with the calculated dipole moments. As shown in Fig. 2, the isomer distribution of **7** is not statistical; the proportions of *e* and *trans*-3 are high (38.1 and 29.5% relative yields, respectively), while those of *trans*-1, *cis*-3, and *cis*-2 are extremely low (below 6% relative yields). This selectivity is also accomplished in the direct reaction from [60]fullerene instead of via **6**. Since there are only small differences in the thermodynamic stability among the seven isolated regioisomers, it is unlikely that the second addition step is under thermodynamic control alone. The observed isomer distribution can be reasonably explained by the combination of the steric factors and the orbital coefficients of the LUMO and LUMO+1 of monoadduct **6**, which accept some electron density from the attacking nucleophile,[6,35,36] as discussed below in more detail. The LUMO has the highest coefficient at the *e*, followed by *trans*-3 and *cis*-2. The observed preference of *trans*-3 over *cis*-2 is apparently ascribable to the lower thermodynamic stability of the latter, with much steric hindrance between addends. Further severe steric repulsion in *cis*-1 ruled out the formation of this isomer.

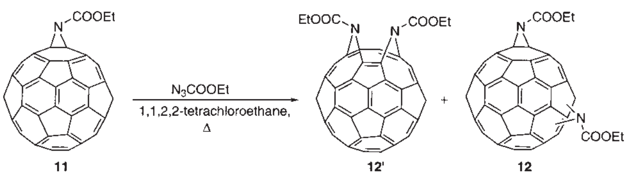
They also examined the reaction of **8** with the diazo compound generated from tosylhydrazone in situ (Eq. 2).[6]



(2)

This reaction probably involves the [3 + 2] cycloaddition of intermediate diazo compound followed by N_2 extrusion in addition to the direct addition of carbene. The regioselectivity in the formation of **9** is analogous to that of **7**. By a similar procedure, Beulen et al. isolated five regioisomers of bisadducts **10** (Chart 1) in a ratio of *trans*-2:*trans*-3:*e*:*cis*-3:*cis*-2 = 14:16:41:5:19.[8]

Hirsch et al. also investigated the addition of nitrene generated from ethyl azidoformate to **11** (Eq. 3).[7]



(3)

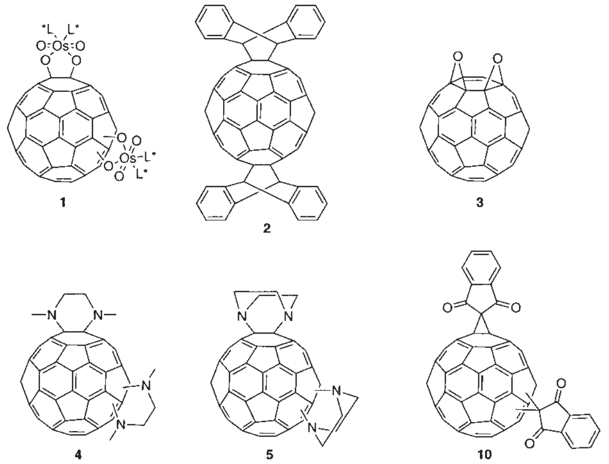
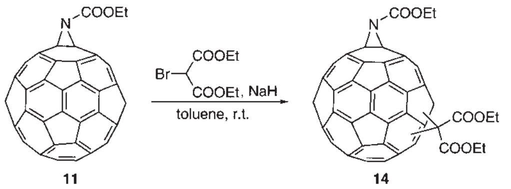


Chart 1.

In this reaction, the *e* isomer of **12** was the most abundant with 27% relative yield. The remarkable difference from Bingel bisaddition in Eq. 1 is that the *cis*-1 isomer **12′** with two open [6,6] junctions was secondly preferred.[7,37] The formation of **12′** apparently indicates less steric hindrance than in *cis*-1 isomer of **7**, which was demonstrated by the AM1-calculated thermodynamic stability; **12′** is more stable than the other isomers by at least 4 kcal mol^{-1}. Noticeably, **12′** was the first example of a fullerene derivative with open transannular [6,6] bonds. On the other hand, the reaction of methyl azidoacetate or trimethylsilylethoxymethyl azide (SEMN$_3$) with [60]fullerene gave bisadduct **13a** or **13b** (Chart 2), in which two neighboring, open [5,6] bonds are imino-bridged.[38] For the latter, **13b** was the exclusive bisaddition product, while a bisadduct whose exact structure was unknown was also obtained for the former.

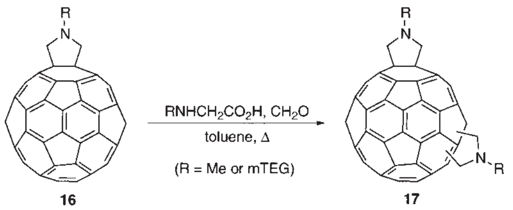
They also prepared bisadducts **14** possessing two different addends by the Bingel reaction with **11** (Eq. 4).[6]



(4)

Since two different *e* isomers are possible due to the presence of different addends, nine isomers of **14** were produced and isolated. The most preferred isomer was *cis*-1, which has two closed [6,6] junctions in contrast with the *cis*-1 of **12′**. The AM1 calculation suggests that the *cis*-1 of **14** with closed form, which is more stable than the open form by 2 kcal mol^{-1}, is the most stable among the nine regioisomers. The isomer distribution in **14** is rather similar to that in **7** except for the formation of *cis*-1. Komatsu et al. examined the Bingel reaction to C_{120}.[39] Among monoadducts **15** (Chart 2), five regioisomers, *trans*-2, *trans*-3, *trans*-4, and two *e*, were isolated and assigned. The relative yields of these isomers were also similar to those for **7**.

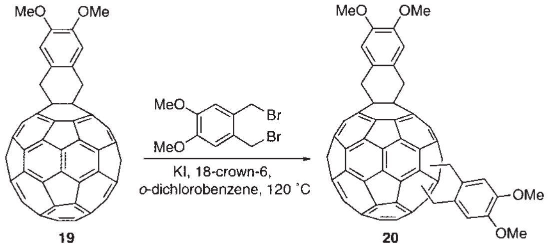
The bisaddition in 1,3-dipolar cycloaddition with azomethine ylide (Prato reaction),[40] one of the most widely applicable reactions for fullerene functionalization, was investigated by several research groups (Eq. 5).[9,10,41,42]



(5)

Recently, all the eight isomers of **17** including *cis*-1 were obtained for R = mTEG (–$CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_3$), as shown in Fig. 2, whereas *cis*-3 and *cis*-1 isomers were not detected in case of R = CH_3.[10,43] For both substituents, the ratios of *e* and *trans*-3 isomers were high, as in the case of Bingel reaction. It is noteworthy that the yield of *cis*-2 was comparable to those of *e* and *trans*-3, suggesting that there is less steric hindrance in the pyrrolidine moieties relative to the malonate esters in Bingel reaction. As a whole, however, the regioselectivity in Prato bisaddition is lower than that in Bingel reaction, as is obvious from Fig. 2. This is mainly due to the extremely high reactivity of intermediate azomethine ylide in Prato reaction. Recently, five regioisomers (*trans*-1 to *trans*-4 and *e*) of **17** (R = H) were prepared and isolated, and their oxidation by MCPBA led to bisnitroxide **17** (R = O•).[44] Irngartinger et al. prepared bisadducts **18** (Chart 2) by the 1,3-dipolar cycloaddition of 2,4,6-trimethoxybenzonitrile oxide with [60]fullerene.[45] Some of possible 22 regioisomers were isolated, but their characterization was not achieved.

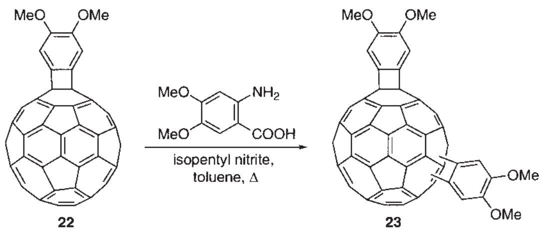
We have examined the bisaddition in Diels–Alder reaction with *o*-quinodimethane species generated from 1,2-bis(bromomethyl)-4,5-dimethoxybenzene and KI (Eq. 6).[21]



(6)

In this case, seven isomers of **20** (not *cis*-1) were isolated by preparative HPLC. The regioselectivity is rather similar to that in the formation of **7** by Bingel reaction, although the *trans*-3 was obtained in preference to the *e* in **20**. The absence of *cis*-1 and the low yields of *cis*-2 and 3 are obviously due to the steric repulsion between the slowly flipping cyclohexene moieties. Mas-Torrent et al. prepared bisadducts **21** (Chart 2) bearing two TTF moieties by a similar Diels–Alder reaction. Seven isomers (not *cis*-1) were produced (*trans*-1:*trans*-2:*trans*-3:*trans*-4:*e*:*cis*-3:*cis*-2 = 3.6:16.1:28.8:2.8:32.0:12.9:3.0), and four of them were isolated by HPLC.[46,47]

The steric hindrance between addends is so severe in Bingel, Prato, and Diels–Alder reactions that the ratios of *cis* isomers are reduced, as described above. Thus, we were stimulated to investigate the bisadditions that have less steric hindrance, in order to correlate the experimental isomer distribution with the coefficients of frontier orbitals based on theoretical calculations more closely. As such reactive species, we paid attention to benzyne, which is known to add to [60]fullerene by [2 + 2] cycloaddition, giving rather rigid adducts.[48,49] The reaction of [60]fullerene with benzyne generated from 4,5-dimethoxyanthranilic acid was examined (Eq. 7).[22]



(7)

As expected, eight regioisomers of **23** including *cis*-1 were isolated by HPLC and could be completely characterized. The regioselectivity for **23** is remarkably different from those in Bingel (**7**) and Diels–Alder (**20**) reactions. The ratio of *cis* isomers in **23** is much higher than that in **7** or **20**. Noticeably, *cis*-1 isomer was obtained in the ratio of 20% second to the *e* isomer, whereas no *cis*-1 isomers were obtained from **7** and **20**. The increased ratio of *cis* isomers can apparently be ascribed to the less steric hindrance in the flat addends of **23**. Such regioselectivity is qualitatively similar to that in the nitrene bisaddition in Eq. 3.

1.2 Theoretical Consideration on Regioselectivity in Bisaddition (Thermodynamic or Kinetic). As mentioned above, while the isomer distribution depends on the nature of reactions or addends to some extent, some characteristic tendencies are observed.

In the bisadditions so far examined and reported, *e* and *trans*-3 isomers are always preferred isomers. However, these isomers have no extra thermodynamic stability according to the calculated heat of formation; in general, the *e* isomer is only slightly more stable than the *trans* isomers, each of which has almost the same stability.[2,6] Therefore, it is unlikely that the selectivity toward *e* and *trans*-3 isomers is derived from a thermodynamic reason.

The relative yield of *cis*-1 is remarkably dependent on the nature (mainly bulkiness) of addends. In **7** carrying two malonate esters and in **20** carrying two cyclohexene rings, no *cis*-1 isomer was produced at all.[2,21] In contrast, the *cis*-1 isomer of **12** (**12′**), **14**, or **23** was the second most abundant, next to the *e* isomer.[6,7,22] Such relative yields are closely associated with the relative thermodynamic stability of *cis*-1. According to MO calculations, the *cis*-1 of **7** is less stable than the others by more than 10 kcal mol^{-1}, while the *cis*-1 is the most stable in the series of **12** and **14**.[2,6,7] The instability of *cis*-1 in the former is apparently derived from the steric hindrance between addends. The *cis*-2 and *cis*-3 isomers of **7** are also less stable than the *e* and *trans* isomers by 1–2 kcal mol^{-1}.[2,6] Thus, the thermodynamic stability of products plays a critical role in the product distribution, at least concerning the formation of *cis* isomers. For tetrahydro[60]fullerene $C_{60}H_4$, the *cis*-1 isomer, which is the thermodynamically most stable, was obtained in the highest yield.[24] Nevertheless, in order to interpret the overall regioselectivity, it is necessary to examine the kinetic aspects.

Since Bingel reaction involves the nucleophile addition of enolate anions from malonate esters, the LUMO and LUMO+1 of the corresponding monoadduct **6** are relevant to the formation of bisadducts **7**. As pointed out earlier, the observed preference for *e* and *trans*-3 isomers is reasonably explained by the high coefficients in LUMO of **6** at these sites.[6,35,36] The much lower yield of *cis*-2 isomer, which could be expected to form in a comparable yield to the *trans*-3 from the consideration of LUMO, results from the fact that the second reactive species is difficult to access to the *cis*-2 positions for the steric reasons. The *e* positions also have high coefficients in the LUMO+1, which is close to the LUMO in energy (0.09 eV). In the LUMO+1, the next high coefficients are observed in the *cis*-1 and *trans*-2 bonds.

In the formation of mixed-bisadducts **14**, which involves the Bingel-type nucleophilic addition toward nitrene-monoadduct **11**, the LUMO and LUMO+1 of **11** are likely responsible for the reaction. Since the LUMO and LUMO+1 of **11** are reported to be quite similar to those of **6**, it is reasonable that the regioselectivity for **14** resembles that for **7**, except for the high yield of *cis*-1 for **14**.[6] The formation of *cis*-1 for **14** is justified by the high coefficient of LUMO+1 at *cis*-1 bonds in **11** and by the high thermodynamic stability of the resulting *cis*-1 isomer of **14**.

Also in the Diels–Alder reaction leading to **20**, it is appropriate to assume some interaction between the LUMO of monoadduct **19** and the HOMO of 4,5-dimethoxy-*o*-quinodimethane. To simplify the calculations, the LUMO of unsubstituted *o*-quinodimethane monoadduct instead of **19** was calculated at PM3 level. This is shown in Fig. 3, which also illustrates the LUMO of $C_{62}(COOMe)_4$ instead of **6**. Both LUMOs are essentially the same; the addend-independency of LUMO has been reported for several monoadducts. Hence, the similarity in the isomer distribution between **7** and **20** is quite reasonable. For **20**, the yields of *cis* isomers are much lower than expected from the LUMO coefficients, due to the steric hindrance between the cyclohexene moieties, as in the case of **7**. The rather lower regioselectivity in **20**, as a whole, is probably derived from the more drastic conditions in the formation of **20** (120 °C) relative to that of **7** (room temperature).

On the contrary, for the formation of **12** or **12′** involving ni-

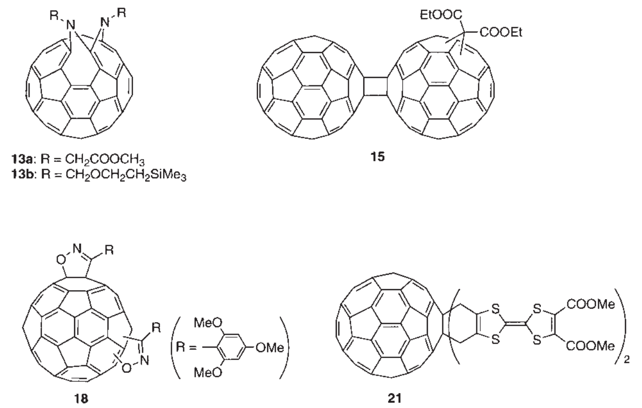


Chart 2.

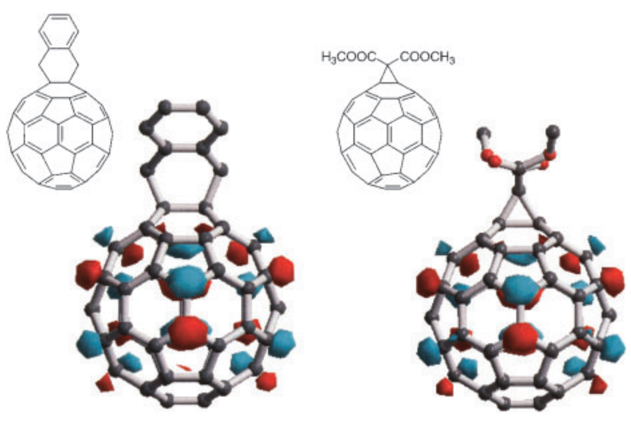


Fig. 3. PM3-calculated LUMO for analogues of monoadducts **6** and **19**.

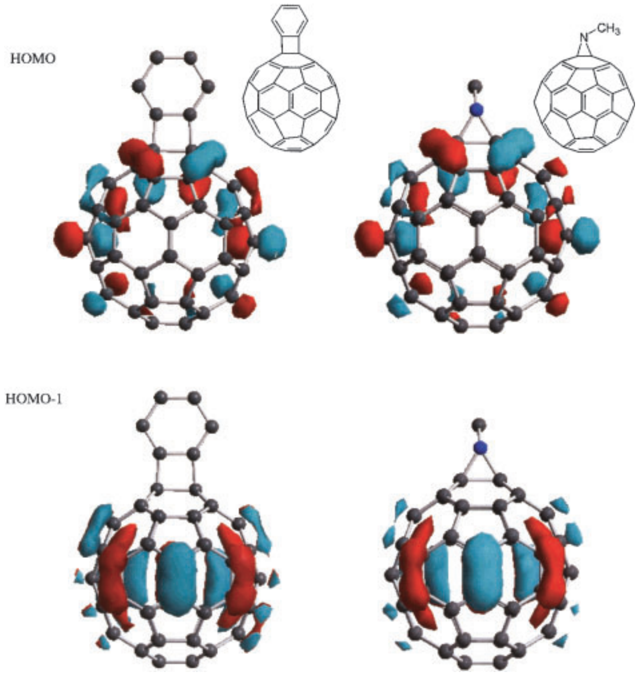


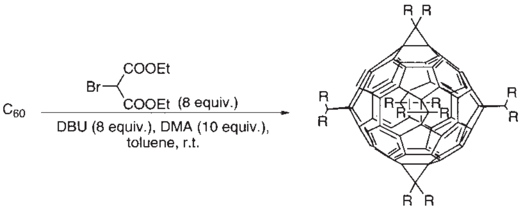
Fig. 4. PM3-calculated HOMO and HOMO−1 for analogues of monoadducts **11** and **22**.

trene addition, it is necessary to examine the HOMO of **11** instead of LUMO. In the HOMO of **11**, which is reported to be quite similar to that of **6**, the highest coefficients are located at *e* sites, followed by the *cis*-1.[6] The coefficients of HOMO−1 are distributed at *e*, *trans*-3, and *cis*-2 bonds, as is observed for the HOMO−1 and LUMO of **6**. These MO structures qualitatively support the isomer distribution of **12** and **12′**. The more severe reaction conditions for **12** and **12′** (145 °C) relative to **7** again led to the less pronounced regioselectivity.

The process of benzyne addition to **22** affording **23** appears to involve the interaction between the HOMO of monoadduct **22** and the LUMO of 4,5-dimethoxybenzyne rather than the reverse combination. The addition is considered to proceed along the mechanism proposed by Fukui et al.[50] Figure 4 shows the PM3-calculated HOMO and HOMO−1 of unsubstituted benzyne monoadduct calculated instead of **22**, along with those of C_{60}(NMe) instead of **11** for the comparison. Both structures are extremely similar to each other. The highest coefficients in the HOMO are located at *e* sites, followed by the *cis*-1, while those of HOMO−1 are at *e*, *trans*-3, and *cis*-2 sites. These characteristics are consistent with the relative yields of bisadduct regioisomers. The tendencies of regioselectivity in **12** (or **12′**) and **23** are similar, including the formation of *cis*-1.

Thus, in order to interpret the regioselectivity in bisaddition, it is useful to examine the LUMO (and LUMO+1) and HOMO (and HOMO−1) of the corresponding monoadducts in the nucleophilic and electrophilic reactions, respectively. Since these frontier orbitals have the highest coefficients at *e* sites, essentially independent of addends, *e* isomers are preferred in both types of reactions. While the high coefficients of *cis*-1 are observed in HOMO and LUMO+1, the relative yield of *cis*-1 isomer was significantly dependent on its thermodynamic stability, closely related with the steric factors of addends.

Anthracene derivatives, which are known to undergo reversible Diels–Alder reactions with fullerenes,[27,51,52] have been utilized as reversible covalent templates, mainly in Bingel reaction.[53–56] Upon addition to [60]fullerene, anthracene derivatives activate the *e* bonds and direct the next addends into these bonds. The use of 9,10-dimethylanthracene (DMA) as a template enabled the efficient formation of T_h-symmetrical hexakisadducts such as **24** with all *e* addition patterns,[53–56] which were obtained in lower yields without templates (Eq. 8).



24: R = COOEt (8)

It is also reported that the use of 2,6-dimethylanthracene enhanced the ratios of *cis*-3 and *cis*-2 bisadducts as well as *e* bisadducts.[57]

1.3 Spectroscopic Methods for Characterization of Bisadducts (Spectroscopic Features). In the early stage of bisadduct synthesis, the isolation and characterization of products was a troublesome task, except for *trans*-1 isomer with the highest symmetry. X-ray crystallographic analysis or sophisticated 2D NMR techniques were required for the assignment of other bisaddition patterns. With the increasing number of bisadducts isolated, however, their spectroscopic features have become disclosed and the characterization of bisadducts has gradually become easier. In most cases, such characterization has been accomplished on the basis of the combination of the NMR and UV-vis spectroscopies and the chromatographic elution order.

The numbers of signals in ^{1}H and ^{13}C NMR spectra are useful for the determination of symmetry. Table 1 summarizes the NMR spectroscopic data of **23** as a representative.[22] The ^{1}H NMR spectrum of D_{2h}-symmetrical *trans*-1 isomer is characterized by only two singlets due to aromatic and methoxy protons. In the ^{1}H NMR spectrum of C_s-symmetrical *e* isomer, in which the mirror plane contains one of the two benzene rings, three singlet peaks with an integral ratio of 2:1:1 are observed for both aromatic and methoxy protons. The other bisadducts afford two aromatic and two methoxy proton peaks, in agreement with C_s or C_2 symmetry. Their addition sites cannot be determined only by the consideration of symmetry in ^{1}H NMR spectra, since C_s symmetry can result from the *cis*-1, *cis*-2, and *trans*-4 and C_2 symmetry from *cis*-3, *trans*-3, and *trans*-2 bisadducts, as depicted in Fig. 1. Theoretically, the number of sp^2 fullerene carbon signals and their intensity patterns in ^{13}C NMR spectra are different in cases of C_2 and C_s symmetry; 28 signals with identical intensity are observed for C_2, while 30 signals including 4 signals with a half intensity are observed for C_s. However, it is usually difficult to distinguish between C_2 and C_s because of the overlapping of some signals. Therefore, only *trans*-1 and *e* are assignable from the symmetry reflected in NMR spectra. Similar be-

Table 1. NMR Spectral Data of Bisadducts **23**[a)]

Compound	Elution order	δ (Ar)[b)]	δ (OMe)[b)]	Number of observed sp^2 ^{13}C signals	Symmetry[c)]
trans-1	1	7.69 (4H)	4.19 (12H)	11	D_{2h} (11)
trans-2	2	7.65 (2H), 7.56 (2H)	4.17 (6H), 4.14 (6H)	33	C_2 (34)
trans-3	3	7.62 (2H), 7.37 (2H)	4.15 (6H), 4.04 (6H)	34	C_2 (34)
trans-4	4	7.48 (2H), 7.33 (2H)	4.09 (6H), 4.02 (6H)	34	C_s (36)
e	5	7.40 (1H), 7.33 (2H), 7.20 (1H)	4.05 (3H), 4.02 (6H), 3.96 (3H)	38	C_s (38)
cis-3	6 or 7	7.35 (2H), 7.26 (2H)	3.96 (6H), 3.93 (6H)	—[d)]	C_2 (34)
cis-2	8	7.50 (2H), 7.26 (2H)	4.16 (6H), 4.00 (6H)	34	C_s (36)
cis-1	6 or 7	7.33 (2H), 7.29 (2H)	4.05 (6H), 3.99 (6H)	34	C_s (36)

a) Measured in $CDCl_3$, except for *cis*-3 in CD_2Cl_2, at room temperature. b) All the signals were observed as singlets. c) Number of theoretical sp^2 ^{13}C signals is shown in parentheses. d) Not available.

Table 2. ^{1}H NMR Spectral Data of Bisadducts **20**[a)]

Compound	Elution order	δ (Ar)[b)]	δ (OMe)[b)]
trans-1	1	7.31 (4H)	4.05 (12H)
trans-2	2	7.29 (2H), 7.22 (2H)	4.04 (6H), 4.01 (6H)
trans-3	3	7.27 (2H), 7.03 (2H)	4.03 (6H), 3.93 (6H)
trans-4	4	7.14 (2H), 7.01 (2H)	3.98 (6H), 3.92 (6H)
e	5	7.07 (1H), 7.06 (2H), 7.01 (1H)	3.97 (6H), 3.94 (3H), 3.91 (3H)
cis-3	7	—[c)]	—[c)]
cis-2	6	—[c)]	—[c)]

a) Measured in 1,1,2,2-tetrachloroethane-d_2 at 120 °C. b) All the signals were observed as singlets. c) Not available.

havior is apparently observed in a series of **20** (Table 2),[21] although their NMR spectra must be measured in 1,1,2,2-tetrachloroethane-d_2 at 120 °C, since the spectra were extremely broadened at room temperature due to the slow flipping motion of the cyclohexene rings.

In the case that a series of bisadduct regioisomers are isolated, the order of chemical shifts in their ^{1}H NMR is helpful for determining the addition sites, since it is closely related to the relative positions of addition sites. Both aromatic and methoxy protons of **23** are deshielded in the order of *trans*-1, *trans*-2, *trans*-3, *trans*-4, *e*, *cis*-3, and *cis*-1.[22] This tendency, ascribable to the different ring currents due to the curvature of the fullerene surface, is also observed in **7**, **17**, and **20**.[9,21] The rather deshielded aromatic protons in *cis*-2 are due to the steric compression effect, as observed in the aromatic protons of some *cis*-2 *o*-quinodimethane bisadducts so far prepared.[21,58] According to the molecular mechanics calculations, the two inner aromatic protons in the *cis*-2 isomer of **23** are located within 2.2 Å. Such situations cannot be accomplished in the other regioisomers, even in the *cis*-3 or *cis*-1 isomer. Furthermore, the ring current effect of benzene rings is also expected to induce the low-field shift of the inner aromatic and methoxy protons in the *cis*-2 isomer. Similar effects may also be involved in the *cis*-1 isomer.

The chromatographic elution order is closely correlated with the addition patterns. In the separation of a regioisomeric mixture of both **20** and **23** using a Deverosil RPFULLERENE HPLC column, the bisadducts were eluted in the order of *trans*-1, *trans*-2, *trans*-3, *trans*-4, *e*, and *cis* isomers, as shown in Tables 1 and 2.[21,22] This elution order apparently corresponds to the positional relationship between the two addition sites; the regioisomers with addends at more remote positions were eluted in earlier retention times. The elution order among *cis*-1, *cis*-2, and *cis*-3 is partly reversed. A similar tendency is observed in the separation of other bisadducts such as **7** and **17**, using silica gel as stationary phase.[2,6,10,59] The correlation between the elution order and addition patterns is quite reasonable if one considers the dipole moments of bisadducts arising from the orientation of addends.

The measurement of UV-vis spectra is the most decisive and facile method for assigning the addition pattern. Figure 5 illustrates the spectra of isomers isolated for **20** and **23** bearing six- and four-membered rings, respectively.[21,22] The similarities between the corresponding regioisomers of both bisadducts are apparent, especially for *trans*-1, *trans*-2, *trans*-3, and *trans*-4. These spectra also resemble those of Prato bisadducts **17** with five-membered rings.[10] In contrast, **7** and **14** with three-membered rings exhibit rather different UV-vis spectra from **17**, **20**, and **23**.[6] These results indicate that the observed UV-vis spectral properties are derived from the π-system of fullerene chromophore which is dependent on addition patterns and almost independent of the nature of addends, although the functionalization by cyclopropanation appears to impose relatively great strain on the fullerene surface and also to allow Walsh-type σ–π interaction, leading to the perturbation of its π-electron system.[60] Thus, UV-vis spectra can be significant and useful tools for the identification of [60]fullerene bisadducts, even though a series of bisadduct regioisomers are not available.

As other unique spectroscopic methods for assigning bisad-

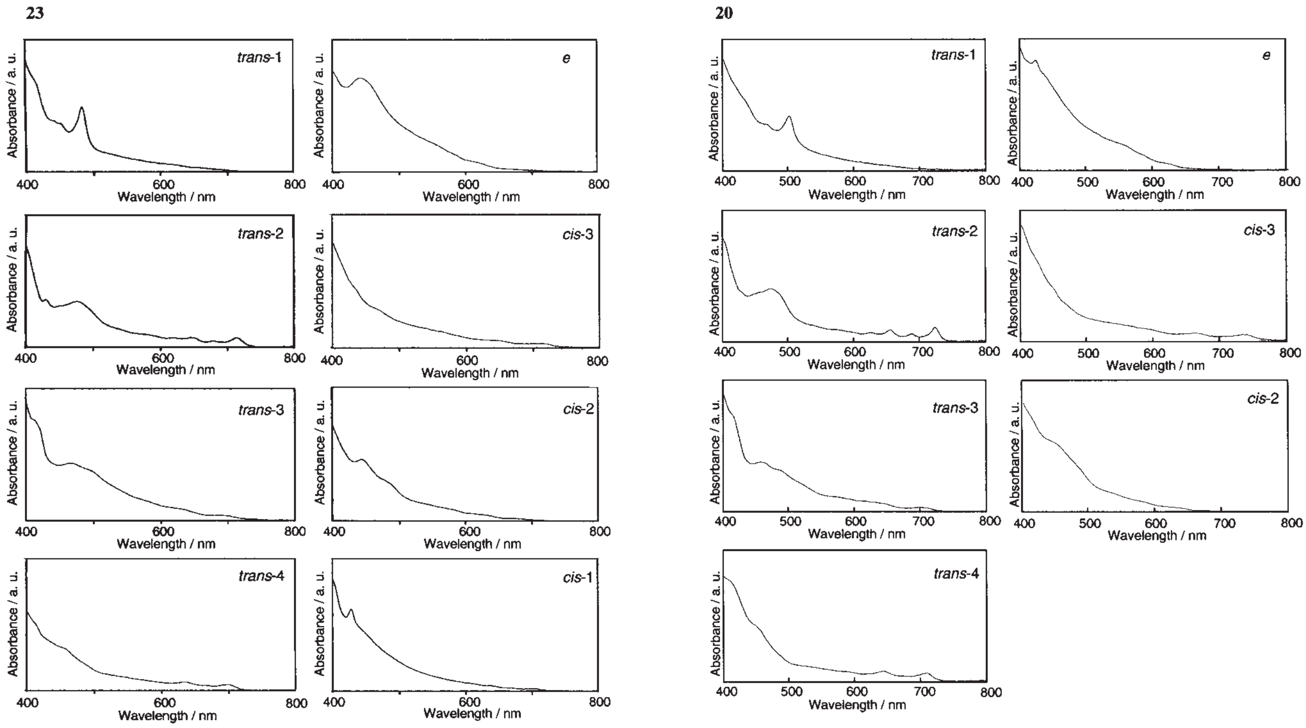


Fig. 5. UV-vis spectra of **20** in carbon tetrachloride and **23** in chloroform.

ducts, ^{3}He NMR spectroscopy has been applicable.[41,61] A ^{3}He atom encapsulated in a fullerene cage is sensitively influenced by the π-electronic ring current of the fullerene cage. The ^{3}He NMR chemical shifts were found to be dependent on the addition patterns for various bisadducts including **7** and **17**. The spectroscopic properties of the excited triplet state have been available. For example, the transient EPR spectra were systematically investigated for the regioisomers of **7** and **17**.[42] The zero field splitting (zfs) parameters (D and E values) and the populations of zero field triplet sublevels were characteristic of each regioisomer. The transient absorption spectra, the quantum yields of triplet formation, and the excited triplet energies were investigated for **7**, **17**, and **20** by using laser flash photolysis.[62–64] These properties also depended on the addition patterns. The properties of excited singlet state were also available. The fluorescence intensity of fullerene derivatives is generally low due to the fast intersystem crossing.[65] The fluorescence spectra of some isomers of **7** were clarified.[65] We have measured the fluorescence spectra of several regioisomers of *o*-quinodimethane bisadducts such as **20**.[63,66] The *cis*-3 and *trans*-4 isomers afforded a relatively distinct emission with a maximum at 745 and 711 nm, respectively, whereas *cis*-2 and *e* only gave quite weak and poorly resolved emissions. The electrochemical properties of bisadducts are also subjects of interest. The electrochemical behaviors of some bisadducts related to **7** and **20** were examined by cyclic voltammetry.[62,66–68] Their redox potentials, which are negative-shifted relative to the corresponding monoadducts, were generally almost independent of addition patterns. Interestingly, electrochemically induced isomerization was observed for **7** by the migration of cyclopropane rings on fullerene surface; a two-electron controlled potential electrolysis (CPE) resulted in the addend rearrangements.[69,70] Regardless of which isomer is used as starting materials, this procedure led to the same isomer distribution and produced larger amounts of bisadducts which are not readily available otherwise; *trans*-1 and *trans*-2 were obtained in 10 and 48% yields, respectively. Some spectroscopic behaviors of radical anions of bisadducts were also investigated. The transient absorption spectra of radical anions of **7** obtained upon pulse radiolysis[62] and the EPR spectra of radical anions of **17** (R = Me or mTEG) prepared by the sodium-reduction[71] were reported. Interestingly, the EPR spectra of radical anions of **21** generated by electrochemical reduction were dependent on addition patterns, whereas those of radical cations of **21** were quite similar among regioisomers.[46] Recently, bisnitroxide radical **17** (R = O$^\bullet$) were also investigated by EPR and ENDOR spectroscopies.[44]

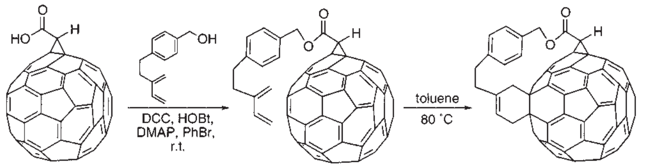
1.4 Optical Resolution of Chiral Bisadducts and CD Spectra of Enantiomers Resolved. As mentioned above, *trans*-2, *trans*-3, and *cis*-3 regioisomers with a C_2-symmetry have a chirality on the π-system of [60]fullerene chromophore derived from their addition pattern. The absolute configuration of each enantiomer is named as $^{f,s}A$ or $^{f,s}C$, according to the recent IUPAC recommendations.[3b] This nomenclature is based on the configurational description (^{f}A or ^{f}C) proposed by Diederich et al.,[72] but the definition of enantiomers is reversed between the two nomenclatures for *trans*-3 and *cis*-3, while both nomenclatures agree with each other for *trans*-2.

The enantiomeric separation of **1**, **7**, **18**, **20**, and **23** with these addition patterns was successful by using preparative HPLC on some chiral stationary phases.[26,58,73–75] Some columns such as Pirkle column, (*R*,*R*)-Whelk-O1, Chiralcel OD, and Chiralpak AD were efficient for the enantioseparation of these bisadducts. The CD spectra of resolved enantiomers were apparently dependent on addition pattern and almost independent of addends, although the band shapes and maximum wavelength for **7** with three-membered rings were rather different from those for **17**, **20**, and **23**. The assignments of absolute configuration were accomplished on the basis of comparisons between the theoretical and experimental CD spectra.[76,77] Therefore, CD spectra are applicable to the determination of *trans*-2, *trans*-3, or *cis*-3 addition pattern and the assignments of absolute configuration.

Interestingly, Nakamura et al. reported the optical resolution of chiral *cis*-3 bisadducts through the formation of diastereomeric α-methoxyphenylacetic acid (MPA) esters instead of using chiral columns.[78] Enantiopure *cis*-3 bisadducts were also obtained by using a tether-constraint method, and their absolute configuration was investigated by computational methods, as mentioned below.[74,75,79]

2. Regioselective Bisaddition by Using Covalent Templates—Mainly Focusing on Diels–Alder Bisaddition

In general, bisadditions without templates afford all possible regioisomers, which are not readily separable. While *e* and *trans*-3 isomers are rather preferentially obtained, other isomers are produced only in poor yields. To obtain such isomers efficiently, the distance and orientation between two reactive species must be regulated so as to be suited for the particular isomers. To this end, tether-directed remote functionalization was successfully exploited by Diederich et al. in 1994 (Eq. 9).[11,80]



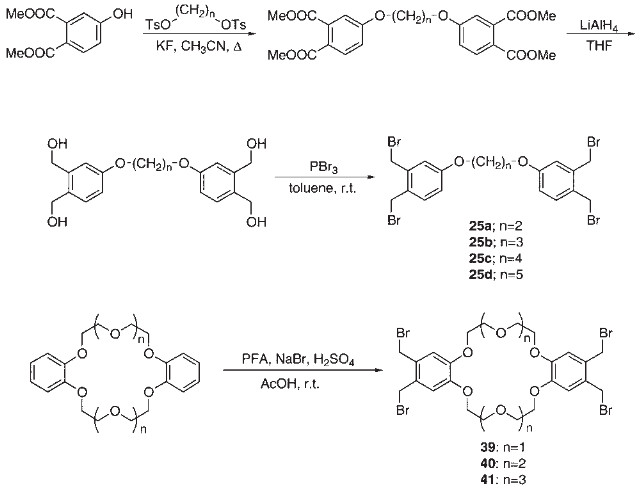
(9)

Since then, a variety of regioselective bisadditions, Bingel reaction,[11] Diels–Alder reaction,[58,66,81–85] [3 + 2] cycloaddition of vinylcarbenes,[79,86] [3 + 2] cycloaddition of azides,[87–91] and [3 + 2] cycloaddition of azomethine ylides (Prato reaction),[92] controlled by covalent templates have been reported. Among them, Bingel bisadditions have been most widely employed, and their versatility is presented in several reviews.[11,12] This account will also contribute to the bisaddition by Diels–Alder reaction, another useful functionalization method for fullerene.

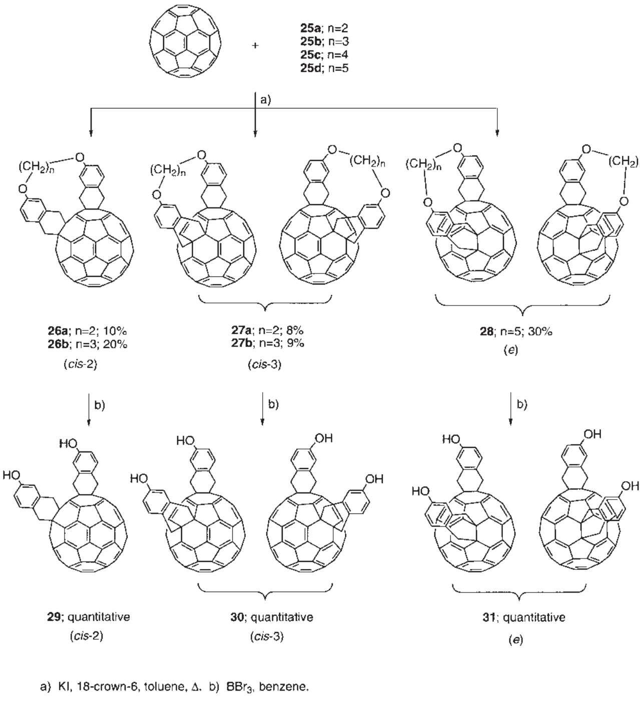
2.1 Diels–Alder Reaction ([4 + 2] Cycloaddition). We have been concerned in the regioselective synthesis of bisadducts by the Diels–Alder reaction with *o*-quinodimethane species. For **20** without templates, seven isomers (not *cis*-1) were produced without satisfactory regioselectivity, although *e* and *trans*-3 isomers were relatively preferred.[21] The ratios of *cis* isomers, especially *cis*-3, were extremely low.

First, we designed α,ω-bis(3,4-bis(bromomethyl)phenoxy)alkanes **25a–d**, which generate *o*-quinodimethane species at both ends of the tether in situ via 1,4-elimination.[58] The resulting regioselectivity is expected to depend on the tether length. The MM2 calculations suggested that the bisaddition can occur only within one hemisphere of [60]fullerene, leading to *cis*-2, *cis*-3, and *e* bisaddition, and the formation of *trans* isomers is excluded.

Bis(*o*-quinodimethane) precursors **25a–d** were prepared starting from dimethyl 4-hydroxyphthalate as shown in Scheme 1.[58] The reactions of **25a–d** with [60]fullerene in the presence of KI and 18-crown-6 were carried out under high-dilution conditions (10^{-4} M), in order to prevent two fullerene molecules from being bridged by the tether of **25** (Scheme 2). While **25c** ($n = 4$) afforded an unseparable complex mixture, other precursors gave one or two products which were readily isolated by column chromatography. With **25a** ($n = 2$), *cis*-2 **26a** and *cis*-3 **27a** were isolated in 10 and 8% yields, respectively. Similarly, **25b** ($n = 3$) regioselectively afforded *cis*-2 **26b** and *cis*-3 **27b** in 20 and 9% yields, respectively. From **25d** ($n = 5$), only *e* isomer **28** was isolated in 30% yield, although slight amounts of other products were



Scheme 1.

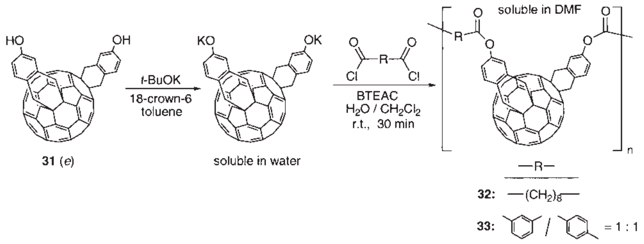


a) KI, 18-crown-6, toluene, Δ. b) BBr_3, benzene.

Scheme 2.

detected. The products obtained were completely characterized by NMR and UV-vis spectroscopies combined with MM2 calculations.

The tethers of all bisadducts were cleaved almost quantitatively by the treatment of excess boron tribromide in benzene at room temperature, to give the corresponding bisphenols **29**–**31**.[58] Naturally, two cyclic bisadducts **26a** and **b** gave the identical bisphenol **29**, and bisadducts **27a** and **b** gave another single product **30**. These bisphenols were applied to the preparation of Langmuir films.[93] Among bisphenols **29–31**, *cis*-3 isomer **30** formed less stable Langmuir films than **29** and **31**. This is ascribable to the lower hydrophilicity due to the intramolecular hydrogen bonding between the OH groups in **30**, as demonstrated by the ^{1}H NMR and IR spectroscopies. Bisphenol **31** was also employed for the synthesis of "pearl-necklace" copolymers.[94] The reaction of **31** with an equimolar amount of dibasic acid dichlorides at room temperature afforded linear polyesters **32** and **33** containing [60]fullerene moieties in the main chain (Eq. 10).

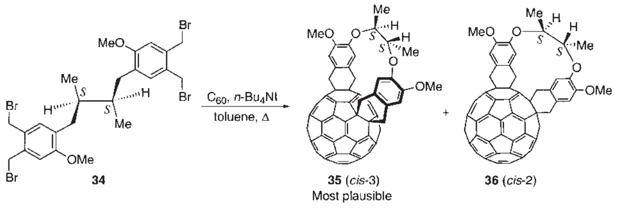


(10)

These polyesters, soluble in DMF, were characterized by the micro ATR-IR spectroscopy and TG analysis. The weight-average molecular weight (M_w) was also determined by the GPC technique.

The racemic mixture of *cis*-3 isomers **27a**,**b** and **30** and *e* isomers **28** and **31** was successfully resolved by a chiral HPLC column (Chiralcel OD).[58,75] The CD spectra of enantiomers of **27a**,**b** and **30**, exhibiting intense Cotton effects derived from the fullerene chromophore modified by chiral addition pattern, are characteristic of *cis*-3 isomers. In contrast, the Cotton effects of **28** and **31** were much smaller than those of **27a**,**b** and **30** due to weak chiroptical contributions. This is because the fullerene addition sites are of locally C_s symmetric T-shape, and the ellipticity is caused only by asymmetrical perturbation due to the oxygen-containing functional groups.

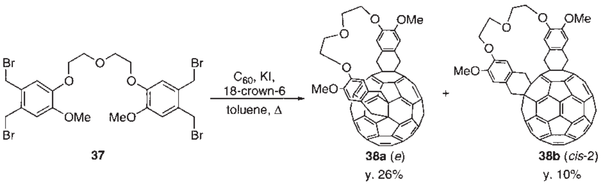
Furthermore, aiming at the diastereospecific synthesis of *cis*-3 bisadducts, a chiral precursor **34** prepared from commercially available (2*R*,3*R*)-2,3-butanediol was allowed to react with [60]fullerene (Eq. 11).[75]



(11)

Besides major *cis*-2 isomer **36**, a single diastereoisomeric *cis*-3 isomer was obtained in 3% yield. The absolute configuration of this isomer, though not definitely determined by MD calculations, was estimated to be **35** from the experimental data on absolute stereochemistry of chiral fullerene bisadducts recently reported by Harada et al.[95]

The regioselectivity from **25a–d** is apparently derived from the constrained distance between the two *o*-quinodimethane species, governed by the oligomethylene linkage. In order to clarify the effects of tether flexibility on the regioselectivity, we have examined the reaction of precursor **37**, which possesses a more flexible oligooxyethylene linkage than the pentamethylene linkage of **25d**.[81] Noticeably, **37** afforded *cis*-2 isomer **38b**, besides the major *e* isomer **38a** (Eq. 12).



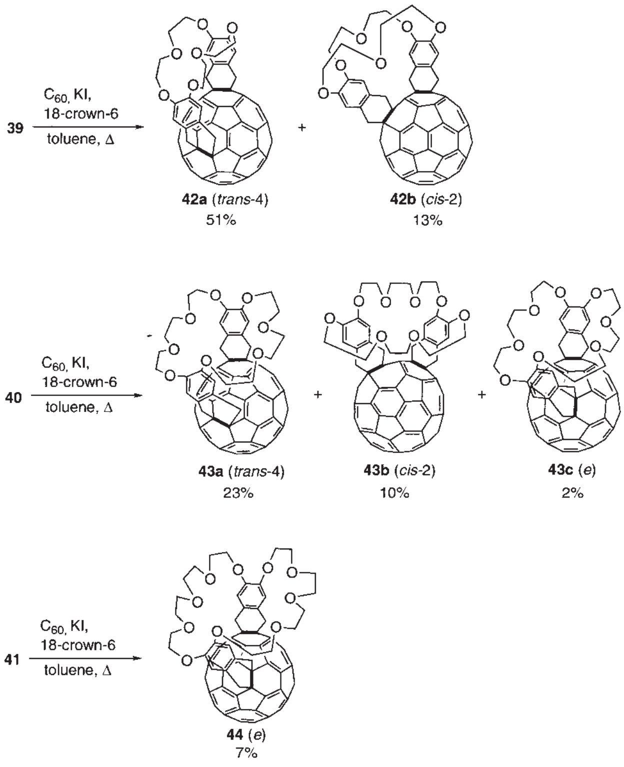
(12)

The formation of the *cis*-2 isomer, which was not obtained from **25d**, is ascribed to the increased flexibility in bridging linkage of **37** due to the C–O ether bond.

For the improvement of regioselectivity, we have also designed the reactions of dibenzocrown ether derivatives such as **39–41**.[66,81] These macrocyclic moieties, which can serve as double bridging linkages connecting two *o*-quinodimethane precursors, are expected to control the relative arrangement as well as distance between the reactive species, probably leading to the preferential addition at two [6,6] sites located almost in parallel. Furthermore, the resulting bisadducts appear to display ionophoric properties different from dibenzocrown ethers themselves.

Precursors **39–41** were prepared from commercially available corresponding dibenzocrown ethers by modifying the method in the literature (Scheme 1).[96] The reaction of [60]fullerene with **39** possessing the smallest 18-crown-6 ring produced *trans*-4 bisadduct **42a** as major product with a relatively high regioselectivity (Scheme 3).[66] From **40** with a medium-sized ring, *trans*-4 bisadduct **43a** was obtained as major product, though the selectivity was lower than that in **39** and a small amount of *e* isomer **43c** was also obtained. On the contrary, **41** with the largest ring exclusively gave *e* bisadduct **44**, similar to **25d** with a single oligomethylene linkage.

The preferential formation of *trans*-4 bisadduct **42a** from **39**, in remarkable contrast with the formation of *e* bisadduct from **25d** or **37**, is quite reasonable, since the dibenzo-18-crown-6 moiety of **39** is expected to force the two *o*-quinodimethane precursors to be almost parallel. The two addition sites of *trans*-4 isomers are located almost parallel, whereas those of *e* isomers are perpendicular to each other. Thus, the *e* bisaddition would significantly distort the crown ether moiety, becoming unfavorable relative to *trans*-4. According to the molecular mechanics calculations (MM2), the *e* isomer derived from **39** has a steric energy higher than *trans*-4 isomer **42a** by more than 20 kcal mol^{-1}. Such a difference led to the selectivity for *trans*-4, though the *e* sites are more reactive than



Scheme 3.

the *trans*-4 sites. Thus, the use of a crown ether unit as double bridging linkages proved to be effective for the regulation of relative arrangement of the two reactive species. The formation of *cis*-2 isomer **42b**, not the *cis*-3 isomer, is a seemingly unexpected result. The steric energy of *cis*-3 isomer is as low as that of *cis*-2 isomer and the two addition sites of *cis*-3 are situated almost parallel, in contrast with *cis*-2 isomer. The selectivity for the *cis*-2 isomer is probably derived from the higher reactivity at the *cis*-2 site than at the *cis*-3 site in the second addition step; this reactivity is evidenced by the higher LUMO coefficients in the corresponding monoadduct determined by the MO calculations (Fig. 3).

The formation of **43a** and **43b** from **40** can be reasonably explained in a manner similar to that for **42a** and **42b**. However, the regioselectivity toward *trans*-4 over *cis*-2 is significantly low compared to **39**, though *trans*-4 still remains the major product. More surprisingly, a slight amount of *e* isomer **43c** was also produced. The reduced selectivity toward *trans*-4 is apparently attributed to the decrease in constraint between two *o*-quinodimethane species due to the enhancement of crown ether ring; since the *cis*-2 and *e* sites are inherently more reactive than *trans*-4, the decreased constraint makes the formation of **43b** and **43c** relatively favorable. The observed isomer ratio seems to reflect the subtle balance between the reactivity of each [6,6] junction and the steric effects resulting from bridging linkages.

Precursor **41** containing a dibenzo-30-crown-10 moiety led to the exclusive formation of *e* isomer **44** without other regioisomers. This selectivity resembles that provided by **25d** with a single linkage rather than **39** or **40** bearing a smaller crown ether moiety. Presumably, the crown ether ring of **41**, sufficiently large and flexible, operates as if it were a single linkage, allowing the second addition to occur at the most reactive *e* position. The increase of size and flexibility in the crown ether moiety makes it difficult to regulate the relative arrangement of two reactive species and to control addition sites.

Table 3 summarizes the properties of tethers in **25**, **37**, and **39–41** and the resulting regioselectivities.[21,58,66,81] The result for the bisaddition without any tether, namely the reaction of [60]fullerene with 4,5-dimethoxy-*o*-quinodimethane (Eq. 6), is also listed for comparison. It is noteworthy that **39** and **40** afforded the *trans*-4 isomer, whose population would be rather low without appropriate tethers, as the major product.

The complexation behavior of these bisadducts with alkali metal ions, mainly investigated by ESI-MS, was different from one to another.[66] For example, **42b** showed only quite weak peaks of $[\mathbf{42b} + \mathrm{M}]^+$ ($\mathrm{M}^+ = \mathrm{Li}^+, \mathrm{Na}^+, \mathrm{K}^+, \mathrm{Rb}^+$, and Cs^+) with any alkali metal ions. In contrast, **42a** afforded all the complexation peaks corresponding to the $[\mathbf{42a} + \mathrm{M}]^+$. The peak of $[\mathbf{42a} + \mathrm{K}]^+$ was observed with the highest intensity, suggesting the highest selectivity of **42a** for K^+ ion. The difference in complexing ability between **42a** and **42b** can be readily explained by the difference in the shape of the diben-

Table 3. Effect of Tethers on Regioselectivity in Diels–Alder Bisaddition

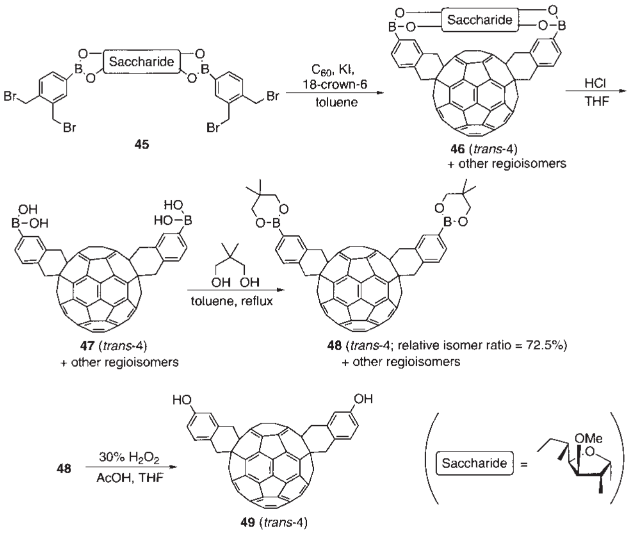
Precursor	Tether			Bisadduct regioisomers obtained[c]	Ref.
	Length[a]	Flexibility[b]	Framework		
25a	4	less	linear	*cis*-2 and *cis*-3	58
25b	5	less	linear	*cis*-2 and *cis*-3	58
25d	7	less	linear	*e*	58
37	7	more	linear	*e* and *cis*-2	81
39	7 × 2	more	cyclic (small)	*trans*-4 and *cis*-2	66
40	10 × 2	more	cyclic (medium)	*trans*-4, *cis*-2, and *e*	66
41	13 × 2	more	cyclic (large)	*e*	66
1,2-bis(bromomethyl)-4,5-dimethoxybenzene	∞	∞	none	*trans*-3, *e*, *trans*-2, *trans*-4, *cis*-2, *trans*-1, and *cis*-3	21

a) Number of atoms constituting tether(s) between two *o*-quinodimethane moieties. b) Flexibility of each tether is mentioned. c) In the order of yields.

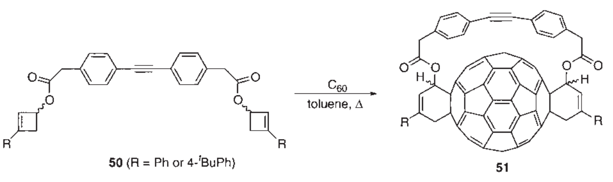
zo-18-crown-6 moiety. Intriguingly, **42a** and **43b** displayed remarkably high selectivity toward K^+ ion; their selectivity coefficients ($K_{Na,K}^{pot}$) toward K^+ over Na^+ ion, determined with an ion-selective electrode, were higher than that of dibenzo-18-crown-6 itself. This high K^+-selectivity suggests a potential application of these bisadducts in biological systems. Thus, the size and geometry of the cavity formed by the crown ether ring depended on the addition pattern and the number of ether oxygen atoms.

As another regioselective synthesis of Diels–Alder bisadducts, Shinkai et al. reported the use of boronate esters composed of two boronic acids and saccharides as imprinting templates.[82,83] The addition sites on [60]fullerene were regulated by the structure of templating saccharides employed. For example, boronate ester **45** containing two *o*-quinodimethane precursors afforded *trans*-4 isomer **46** as the major product (Scheme 4). The saccharide template of **46** was removed to give boronic acid **47**, which can serve as the selective receptor for the original saccharides. After the protection of boronic acid groups of **47**, the resulting **48** was transformed into bisphenol **49**, which is a regioisomer of **29–31**, by the treatment with H_2O_2. They also reported the regioselective synthesis of bisadducts using steroid templates.[84]

Rubin et al. succeeded in the selective preparation of *trans*-1 bisadducts by the Diels–Alder reaction with rigid 1,3-butadiene derivatives.[85] Without templates, this isomer is generally least likely to form from both statistical and kinetic aspects. Also, in the covalently templated Diels–Alder bisadditions described above, *trans*-1 isomer was not accessible. Bis(cyclobutene) **50**, designed to prefer this isomer based on AM1 calculations, was refluxed in toluene to generate 1,3-butadiene intermediates, which reacted with [60]fullerene to afford *trans*-1 bisadduct **51** as a diastereoisomeric mixture (Eq. 13).



Scheme 4.



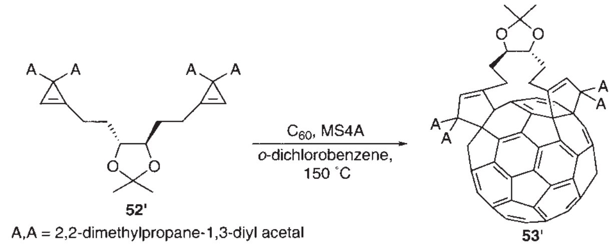
(13)

Compound **51**, whose tether can be readily eliminated, was further applicable to the formation of mixed hexakisadducts.

2.2 [3 + 2] Cycloaddition of Vinylcarbenes. Nakamura et al. prepared bis(cyclopropenone acetal) **52**, which generates vinylcarbenes upon thermolysis.[79,86] These intermediates underwent [3 + 2] cycloaddition with [60]fullerene to give bisadducts **53** (Eq. 14).

(14)

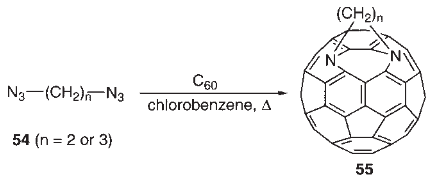
Their addition sites showed remarkable dependence on the tether length. With **52** ($n = 3$), both *cis*-1 and *cis*-2 isomers were obtained, while **52** ($n = 4$) exclusively provided *cis*-1 isomer. Although **52** ($n = 5$) gave no isolable bisadducts, **52** ($n = 6$) afforded *cis*-3 isomer as a single product. It was suggested that the conformational strain in the transition state rather than the product stability controls the regioselectivity, based on the computational studies. Thanks to application of this reaction, the synthesis of non-racemic *cis*-3 isomer with C_2 symmetry was also successful (Eq. 14′).



(14′)

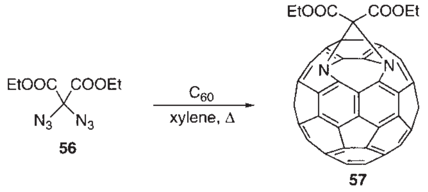
From **52′** containing a chiral tether, a single diastereoisomerically pure *cis*-3 isomer **53′** was obtained.

2.3 [3 + 2] Cycloaddition of Azides. The attack of alkyl azides toward [60]fullerene, followed by N_2-extrusion, usually affords azafulleroids with [5,6]-open structure. Luh et al. prepared tethered bis-azides **54** ($n = 2, 3$), which were allowed to react with [60]fullerene (Eq. 15).[87]



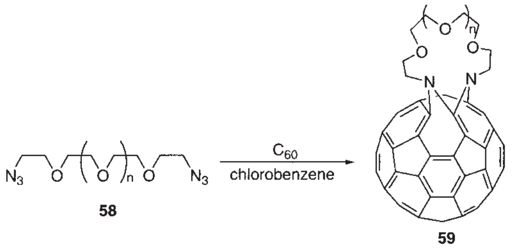
(15)

In both cases, bisazafulleroids **55** were selectively obtained, in which two [5,6] junctions within the same five-membered ring are nitrogen-bridged. Dong et al. successfully synthesized the similar bisadduct **57** from diethyl diazidomalonate **56** (Eq. 16).[88]



(16)

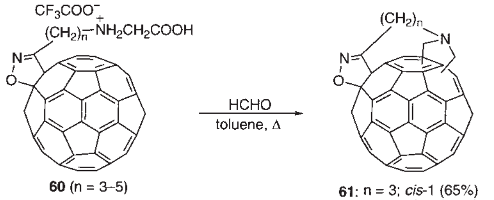
Ikeda and Shinkai examined the reaction of bis-azides **58** with a longer and more flexible linkage (Eq. 17).[89]



(17)

These precursors afforded bisazafulleroids **59**, in which two neighboring, open [5,6] bonds are imino-bridged similar to **13**. Analogous reactions were also reported by Chen et al.[90] Intriguingly, Rubin et al. succeeded in the effective opening of fullerene cage by the reaction using a rigid bisazidobutadiene derivative.[91]

2.4 [3 + 2] Cycloaddition of Azomethine Ylides. Prato et al. designed isoxazolinofullerene derivatives **60** ($n = 3$–5) carrying a glycine residue linked by an oligomethylene linkage.[92] The treatment of **60** with formaldehyde generated azomethine ylides, which afforded fulleropyrrolidines **61** by the [3 + 2] cycloaddition (Eq. 18).

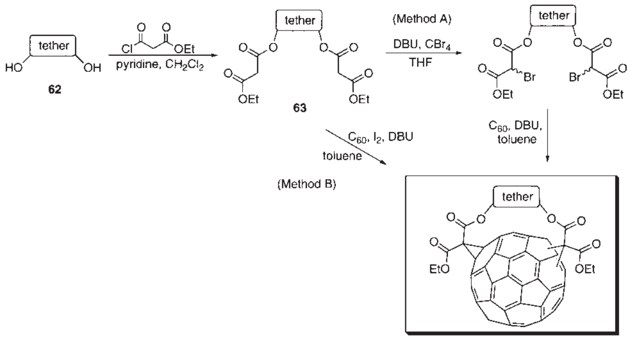


61: n = 3; *cis*-1 (65%)
n = 4; *cis*-1 (67%)
n = 5; *cis*-1 (54%), *cis*-3 (31%), *cis*-2 (2%)

(18)

With $n = 3$ and 4, the *cis*-1 isomer of **61** was isolated as a single main product. In contrast, for $n = 5$, *cis*-2 and *cis*-3 isomers were also produced besides the major *cis*-1 isomer. The formation of three isomers is ascribed to the increased freedom due to the longer aliphatic chain.

2.5 Bingel Reaction and Related Reactions. The double Bingel reactions of [60]fullerene with bismalonate derivatives linked by a variety of tethers have been extensively reported.[11,12] This methodology is quite versatile for the regioselective and diastereoselective preparation of bisadducts. Scheme 5 depicts the general synthetic sequence of double Bingel reactions. Tethered diols **62** are first treated with ethyl malonyl chloride to give the corresponding bis(ethyl malonate) derivatives **63**. Subsequently, two methods are employed, depending on whether the corresponding halomalonates are isolated (Method A)[5] or only generated in situ (Method B).[97] More frequently, the latter is employed; the one-pot reaction of **63**, [60]fullerene, I_2, and DBU usually affords the desired bisadducts in reasonable 20–40% yields. With this method, seven bisaddition patterns except for *cis*-1 have so far been accomplished. Several examples for each addition pattern are summarized in Scheme 6.[67,68,74,98–101]



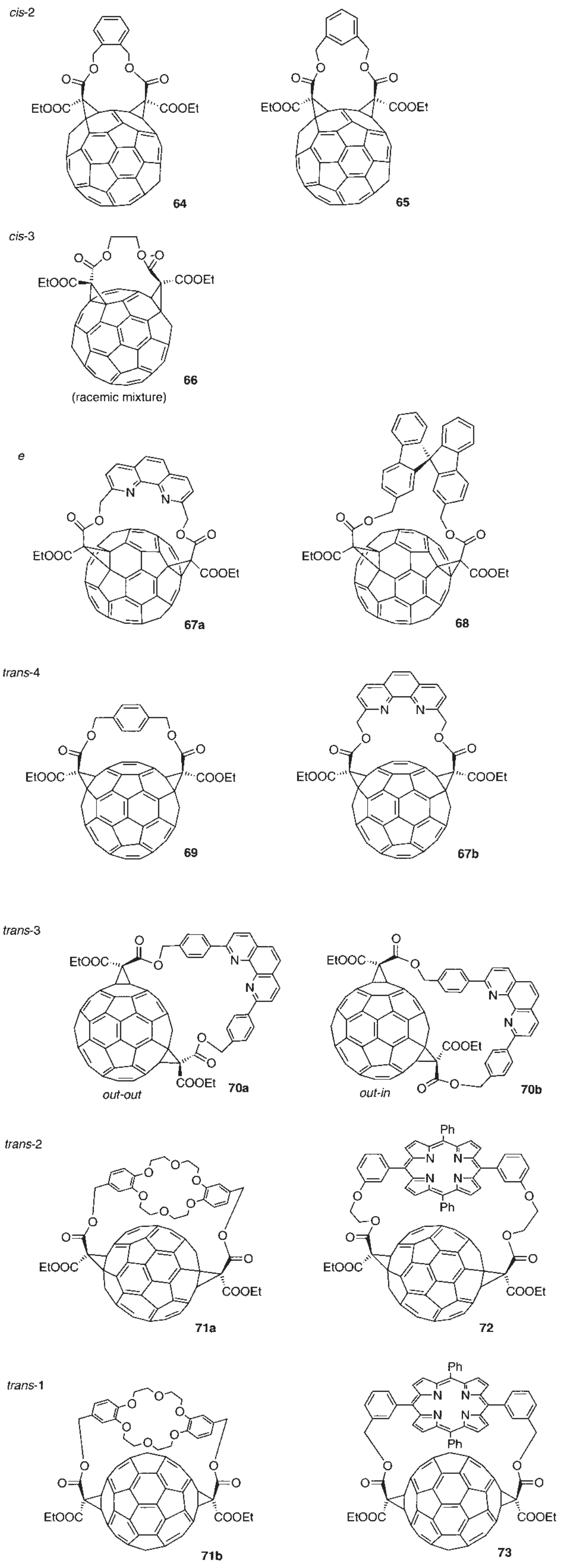
Scheme 5.

For each regioisomer, there are several possible diastereoisomers arising from the differences in the orientation of ethoxycarbonyl residues, as experienced in *o*-quinodimethane bisadditions.[58] For instance, *cis*-2 isomers provide three diastereoisomers, *out–out*, *in–in*, and *in–out*, as illustrated in Scheme 7. In practice, however, *out–out* isomers are exclusively produced, except for the formation of *in–out* for **70b**.[98]

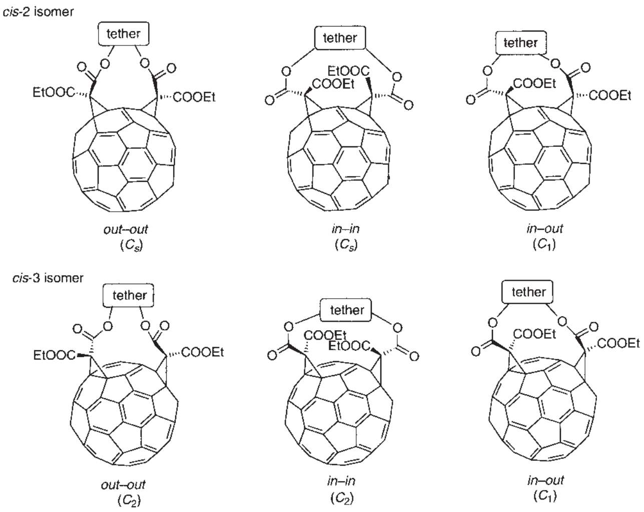
Diederich et al. also performed diastereoselective synthesis of *cis*-3 bisadducts by using a chiral tether (Scheme 8).[99] Bismalonate (R,R)-**74**, prepared from the optically pure diol, afforded $(R,R,{}^{\mathrm{f,s}}A)$-**75** with a high diastereoselectivity (d.e. > 97%). This selectivity is derived from the stability of $(R,R,{}^{\mathrm{f,s}}A)$-**75** relative to the corresponding diastereoisomer $(R,R,{}^{\mathrm{f,s}}C)$-**75** by ca. 5 kcal mol^{-1}. Similarly, (S,S)-**74** diastereoselectively provided $(S,S,{}^{\mathrm{f,s}}C)$-**75**. Bismalonate (R,R)-**76** derived from conformationally more rigid (R,R)-*trans*-cyclohexane-1,2-diol enabled the regio- and diastereoselective formation of *cis*-3 bisadduct **77** in higher yield.

Quite recently, the reactions of macrocyclic bismalonates **78a–e**, readily prepared from alkanediols and malonyl dichloride, were investigated.[102] Although a complex mixture was obtained from **78a**, other bismalonates regioselectively afforded specific bisadducts **79b–e** depending on the chain length, as shown in Scheme 9. This method was applied to the regioselective synthesis of tris- and tetrakisadducts, and the novel *trans*-4,*trans*-4,*trans*-4-trisadduct was first isolated and characterized. It was proposed that the resulting addition pattern is closely related to the symmetry involved in the starting malonates **78**; precursors containing chains of identical length afford addition patterns with rotational symmetry (C_2 or C_3), while those with different spacer lengths yield bisadducts with C_s symmetry such as *cis*-2 or *e*.

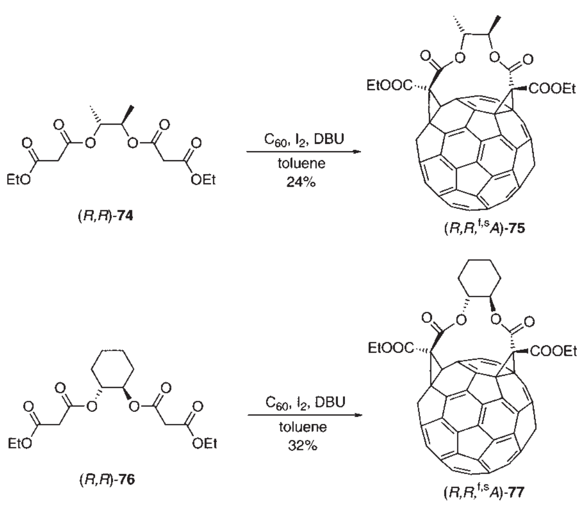
The regioselective bisadditions using active methylene compounds other than malonate esters were also reported. For ex-



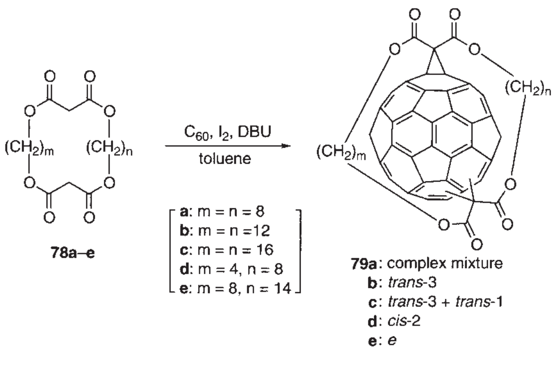
Scheme 6.



Scheme 7.

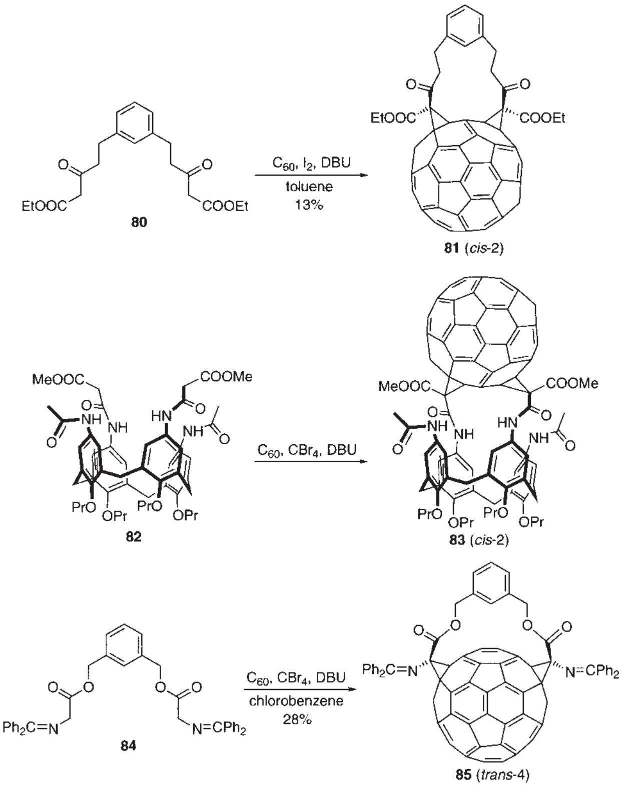


Scheme 8.

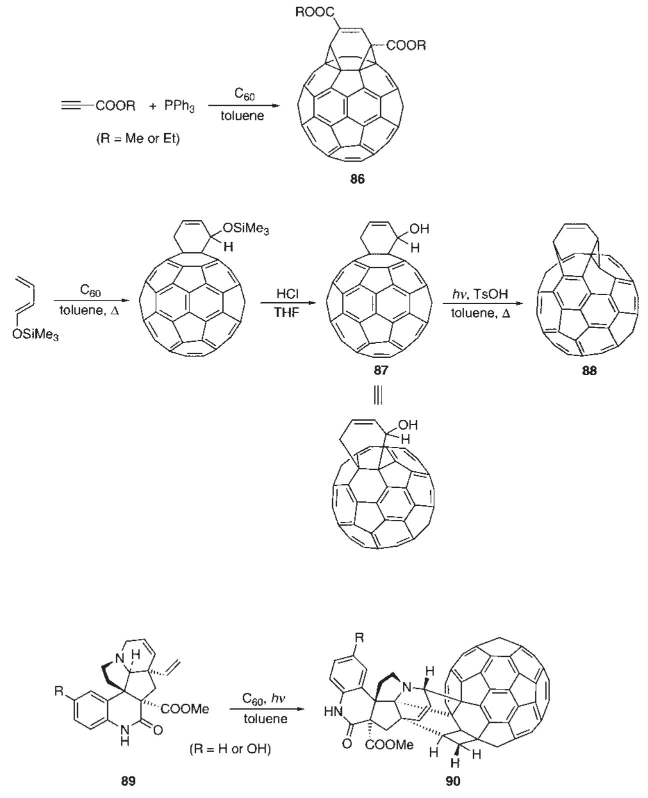


Scheme 9.

ample, *m*-phenylene-bridged bis(β-keto ester) **80** gave *cis*-2 isomer **81** regioselectively, similar to the formation of **65** from the bismalonate (Scheme 10).[103] Calix[4]arene derivative **82** bearing two malonamide moieties also led to the formation of *cis*-2 bisadduct **83** as fullerene-calixarene conjugate, regarded as a molecular counterpart of the football world cup.[104] Interestingly, bis(imino-glycine) **84** produced *trans*-4



Scheme 10.



Scheme 11.

isomer **85** as the major product along with a small amount of *cis*-3 isomer.[105] This regioselectivity is in a remarkable contrast with that for **65** and **81**, in spite of using similar precursors.

2.6 Miscellaneous. Treatment of methyl or ethyl propiolate with [60]fullerene in the presence of triphenylphosphine in toluene afforded *cis*-1 bismethanofullerene **86**, in which the two methano groups are attached to the [6,6] bonds within a six-membered ring (Scheme 11).[106] On the other hand, the photolysis of **87** under reflux and acidic conditions gave bisfulleroid **88** possessing two open [5,6] bonds within a six-membered ring.[107] Furthermore, Rubin et al. succeeded in the preparation of tetrakisfulleroids by developing this method.[85c] Bisfulleroids similar to **88** were also obtained by the photolysis of cyclohexadiene-fused fullerene derivatives.[108] Intriguingly, the photochemical reaction of scandine or its derivative **89** with [60]fullerene afforded novel monoadduct **90**, which is regarded as *cis*-1 bisadduct.[109]

3. Concluding Remarks

Bisadditions to [60]fullerene generally afford (almost) all of the possible eight regioisomers, *trans*-1 to -4, *e*, and *cis*-3 to -1. The regioselectivity in bisaddition is closely related to the LUMO (and LUMO+1) and HOMO (and HOMO−1) coefficients of the corresponding monoadducts in the cases of nucleophilic and electrophilic reactions, respectively, although the relative yield of *cis*-1 isomer is significantly dependent on its thermodynamic stability, based on the steric factors of addends. The isolation and characterization of bisadducts have become feasible with the developments of chromatographic separation techniques as well as spectroscopic methods. Their electronic and photophysical properties are characteristic of addition patterns, almost independent of the nature of addends. Especially, *cis*-3, *trans*-3, and *trans*-2 isomers with a chirality on the [60]fullerene π-electron system are also of interest from their chiroptical aspects.

To enhance the regioselectivity in bisadditions, a synthetic methodology was developed with using tethers as covalent templates. The distance and orientation between two reactive species were efficiently constrained by tethers, allowing the formation of specific isomers depending on their structure. All bisadduct isomers, from *trans*-1 to *cis*-1, have so far been available by the appropriate combination of various tethers and reactive species. In general, these tethers are readily removable from the resulting tethered bisadducts, and then further functionalization including the construction of supramolecular species is possible, aiming at the applications into advanced functional materials.

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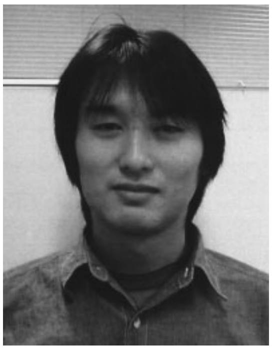

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