REGIOSELECTIVE CHEMICAL MODIFICATIONS OF C_{60} FULLERENES

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INTRODUCTION

[60]Fullerene (C_{60}) was first isolated from vaporized graphite by Krätschmer and Huffman in 1990 and later found to have an aromatic structure with a soccer-ball-like shape.[1,2] Early functionalization studies of C_{60} revealed that this carbon allotrope can undergo a variety of chemical reactions characteristic of electron deficient polyolefins.[3] [60]Fullerene consists of twelve pentagonal rings that are isolated by twenty hexagonal ones where all the double bonds are located as shown in its lowest energy resonance form. Accordingly, the [6,6] bonds have greater double bond character and are shorter than [5,6] bonds. The [6,6] bonds are thus used to functionalize C_{60} by nucleophilic, radical additions, as well as cycloadditions. In 1994, the development of tether-directed remote functionalization of C_{60} by Diederich and co-workers became the first rational approach toward the regioselective synthesis of three-dimensional C_{60} derivatives.[4] Subsequently, a considerable number of multiple adduct patterns were achieved that could be performed without extensive purification protocols.

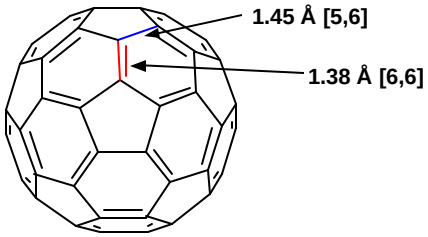


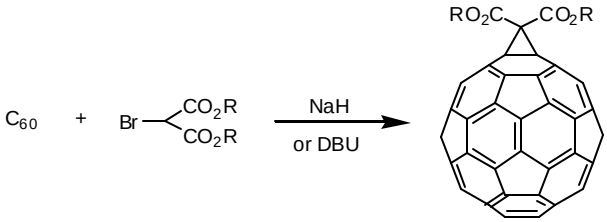
Figure 1. Structure of a [60]fullerene molecule with two characteristic bonds

The discovery that C_{60} derivatives have biological activity, such as HIV-protease inhibition[5], photodriven DNA cleavage[6], radical scavenger[7], leads to the creation of a rapidly expanding new area of fullerene science.[8] Fullerenes are highly hydrophobic; water-solubility can be achieved by attaching polar functional groups onto the fullerene structure. Moreover, regio- or stereochemically defined three-dimensional multifunctionalized fullerene structures are particularly important for biological applications, such as molecular recognition. This report reviews the regioselective chemical modifications of fullerenes and includes some biological applications of water-soluble C_{60} derivatives.[9]

BINGEL CYCLOPROPANATION REACTION

The Bingel cyclopropanation reaction is an efficient tool for the regioselective functionalization of C_{60} derivatives.[10] Treatment of C_{60} by 2-bromomalonate esters in the presence of a non-nucleophilic base, such as NaH or diazabicyclo[5.4.0]undec-7-ene (DBU), gave cyclopropane derivatives (Scheme 1). The advantages of this method are: (i) exclusive addition on [6,6] double bonds of the fullerene skeleton, (ii) mild reaction conditions giving relatively high yields, (iii) installation of ester moieties that allow additional chemical transformations. Alternative strategies to generate reactive monohalomalonate intermediate in situ have been reported by Hirsch and Diederich.[11] Carbanionic precursors other than malonates (e.g., sulfur ylides) have also been used to obtain corresponding methanofullerenes following a similar addition-elimination pathway.[12] This simple methodology to functionalize fullerenes has allowed C_{60} to be used for the construction of novel materials.

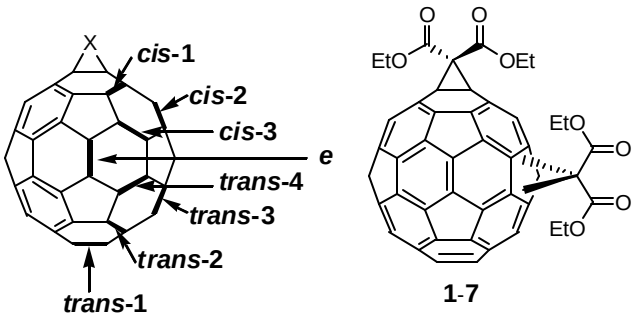
Scheme 1. The original Bingel reaction



TETHER-DIRECTED DOUBLE AND TRIPLE BINGEL ADDITIONS

Sequential double addition

Although the Bingel protocol has been demonstrated successful in mono-functionalization of [60]fullerene, the multiple functionalization of fullerenes by Bingel addition remains problematic due to the non-selective formation of regioisomers. By sequential reaction of two Bingel additions, Hirsch and coworkers obtained seven out of eight possible bisadducts with *cis*-2, *cis*-3, *e*, *trans*-1, *trans*-2, *trans*-3, and *trans*-4 patterns (*cis*-1 pattern was not formed due to steric hindrance) (Figure 2). The *e* and *trans-3* bisadducts are most favorable, with 15.5% and 12.0% yield, respectively, although isolation required tedious chromatographic separation.[13] The favorable *e* and *trans-3*



(*cis*-1); 0%
1 (*cis*-2); 0.9%
2 (*cis*-3); 2.5%
3 (e); 15.5%
4 (*trans*-4); 3.7%
5 (*trans*-3); 12.0%
6 (*trans*-2); 5.3%
7 (*trans*-1); 0.8%

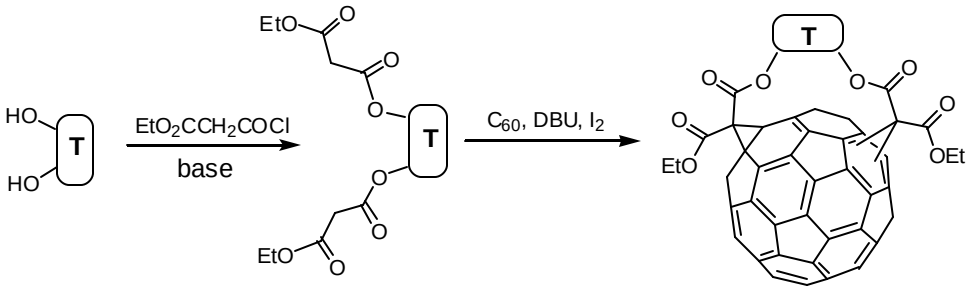
Figure 2. Position notation for bismethanoadducts of C_{60}

additions are in good agreement with molecular orbital calculations.[14]

Tether-directed double Bingel cyclopropanations

In 1994, a general approach for the tether-directed double Bingel cyclopropanation was proposed by Diederich and coworkers (Scheme 2).[15] This approach involves reaction of C_{60} with a tether-connected bismalonate in the presence of I_2 and DBU. The corresponding 2-iodo-malonate was generated in situ and subsequently reacted with C_{60}. Tether-directed remote functionalization gave improved yields and regioselectivity.

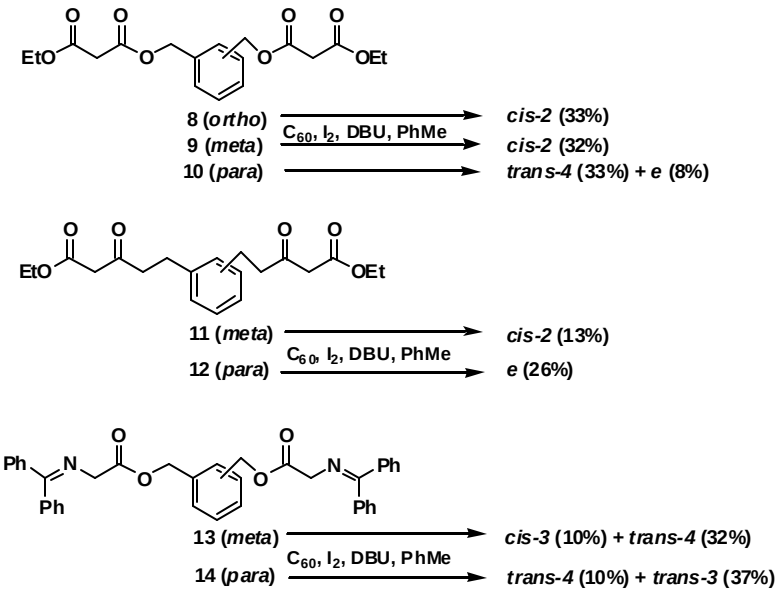
Scheme 2. General scheme of the tether-directed double Bingel reaction of bismalonates with C60



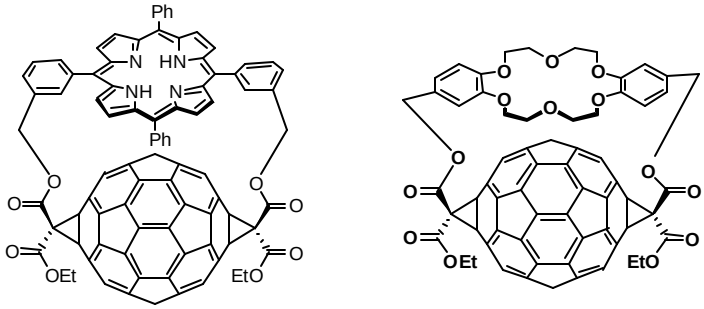
Tethers and related spacers

Among various tethers, xylylene linkers are the simplest and are already widely used type for construction of amphiphilic Langmuir-Blodgett thin films.[16] Diederich and coworkers reported that the regioselectivity of addition strongly depends on the ortho-, meta-, or para- substitution patterns of the benzene tether. In situ generated bis-iodomalonates derived from *o*-xylene **8** and *m*-xylene **9** afforded exclusively *cis*-2 bisadducts, whereas para-analog **10** yielded primarily *trans-4* bisadduct and a minor amount of racemic *e* regioisomer (Scheme 3).[15] Interestingly, they also found that the product ratio of the para-analog varied with different halogen leaving groups. Additionally, when changing bismalonate to tethered keto esters and imino esters, regioselectivity patterns varied, indicating the addition dependence on the activated methylene forms.[15]

Scheme 3. Double Bingel addition by xylylene and xylylene derivative tethers



The success of tethering methods can be also attributed to its facile access to kinetically disfavored addition patterns not easily accessable by sequential addition method, such as *trans*-1.[17] Diederich and coworkers obtained the *trans*-1 bisadduct **15** in 17% yield by using a porphyrin-bismalonate tether. Dibenzo crown ether tether afforded *trans*-1 bisadduct (±)-**16** in a higher yield of 30% with a minor amount of *trans*-2 isomer (Figure 3).[18] Interestingly, K^+ ion complexation to the crown ether further enhanced the regioselectivity and yield, allowing *trans*-1 bisadduct to be obtained exclusively in a remarkable 50% yield. This finding demonstrates that a more rigid spacer increases the selectivity of the second addition.[19] In contrast, zinc (II) complexation of porphyrin did not enhance regioselectivity or yield since metal coordination inside the porphyrin ring has little effect on the rigidity of tether.

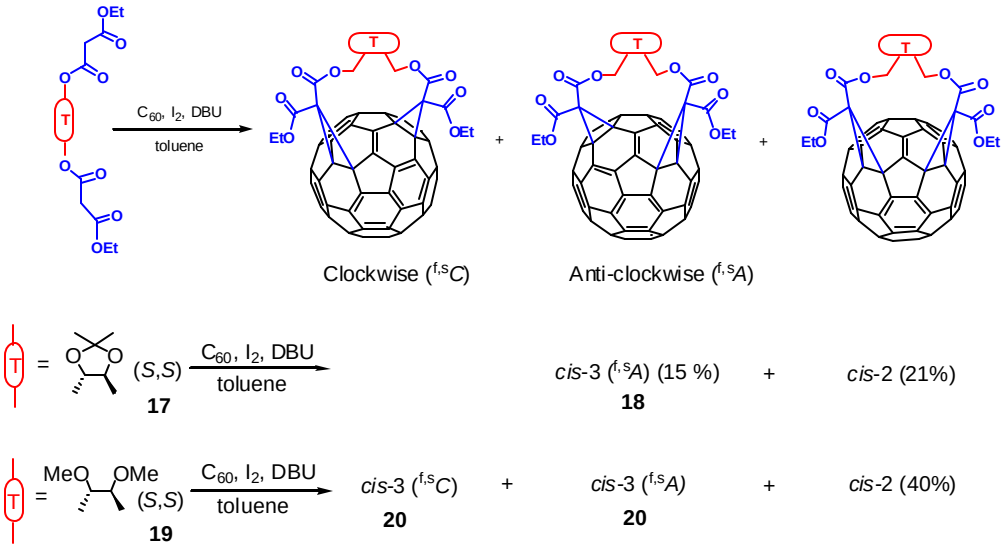


15 (*trans*-1) (±)-**16** (*trans*-1)

Figure 3. Porphyrin-fullerene and crown ether-fullerene conjugates prepared by double Bingel reaction

Among the eight bisaddition patterns (*cis*-1, *cis*-2, *cis*-3, *e*, *trans*-1, *trans*-2, *trans*-3, and *trans*-4), the three inherently chiral addition patterns, *cis*-3, *trans*-2, and *trans*-3 are of particular interest. These C_{60} bisadducts must be both regio- and diastereoselective to produce optically active C_{60} derivatives. The first asymmetric synthesis of *cis*-3 bisadduct of C_{60} employed an enantiomerically pure bismalonate (*S*, *S*)-**17** derived from threitol. Enantio pure *cis*-3 bisadduct (*S*, *S*, ^{f,s}*A*)-**18** (f=fullerene, s=systematic, *C*=clock-wise, *A*= anti-clockwise) was obtained in 15% yield.[15] The exclusive formation of the single diastereomer results from the direction of the chiral tether toward one of the two chiral adducts. An open-chain threitol derivative (*S*, *S*)-**19** was used for a comparison study to further explore the effect of the dioxolane ring structure on the chiral tether. The two diastereoisomeric products (*S*, *S*, ^{f,s}*C*)-**20** and (*S*, *S*, ^{f,s}*A*)-**20** were formed with relatively poor diastereoselectivity in a ratio of

Scheme 4. Synthesis of chiral Bingel-type bisadducts of C_{60}

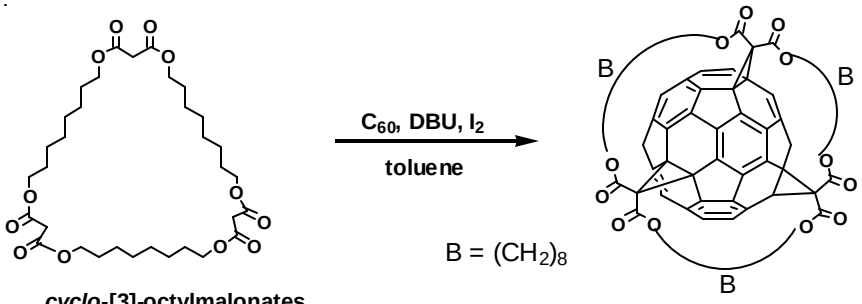


1:2.5, indicating the importance of a structurally well defined tether.[15]

Macrocycle-templated synthesis of water-soluble *e, e, e* - hexaacid

Although the tether method gives good yields and regioselectivity, the linker can be difficult to synthesize. Thus, a facile building block approach is desirable. Hirsch and coworkers reported a flexible cyclooligomalonate template for convenient synthesis of bis- to hexakisadducts.[20] The macrocycle template was synthesized by reaction of the corresponding diol with malonyl dichloride in a 1:1 ratio and adducts were then purified with chromatography. The success of this approach was demonstrated by the facile synthesis of a *e, e, e*-hexaacid **23**, which could be otherwise obtained with 9% yield by using a trivalent tether.[21] In contrast, the reaction of *cyclo*-[3]-octylmalonate **21** with C_{60} afforded *e, e, e* isomer **22** with rotational symmetry in a crude yield of 94% relative to 6% of the *trans*-4, *trans*-4, *trans*-4 isomer (Scheme 5).

Scheme 5. Macrocyclic oligomalonates templated synthesis of *e*, *e*, *e*-hexaacid

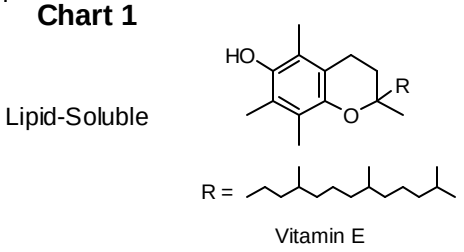


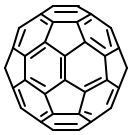
***cyclo*-[3]-octylmalonates**
21

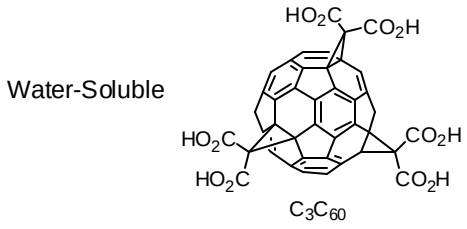
(±)-**22** (*e*, *e*, *e*)

Saponification of trisadduct **22** afforded pure *e, e, e*-hexaacid **23**, which exhibits water solubility at a pH = 7.[22]

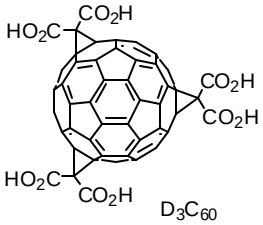
Chart 1







23



24

Water-soluble *e,e,e*-hexaacid **23** has potential as an antioxidant drug. Indeed, it is a stronger radical scavenger against lipid peroxidation than vitamin E due to its multiple C=C bonds that act as radical receptors.[23] Shown in Chart 1 are four compounds divided into two categories: lipid-soluble (top) and water-soluble (bottom), and they were examined by Hwang and coworkers for their protection effects. The radical species were generated with Fenton's and the xanthine-xanthine oxidase enzyme reaction. A pH-sensitive dye, 8-hydroxypyrene-1,3,6-trisulfonic acid trisodium (HPTS), which has two strong UV absorbance at 403 and 454 nm was used as an indicator to report membrane leakage. Upon membrane leakage, the relative ratio of

A_{453} vs A_{403} increases, and a higher ratio indicates more lipid peroxidation leading to membrane leakage.

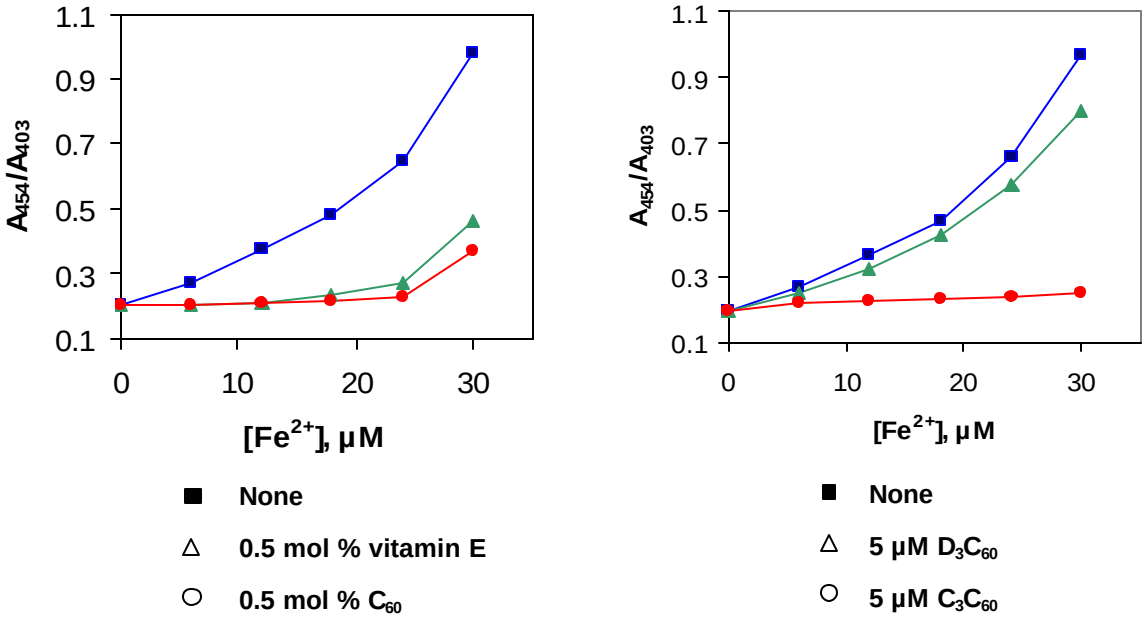


Figure 4. Absorbance ratio A_{454}/A_{403} as a function of the concentration of $FeSO_4$

For lipid-soluble antioxidants, the membrane leakage decreases in the sequence: liposome > vitamin E > C_{60}, and **24** > **23** for water-soluble antioxidants (Figure 4). The combination of the water-soluble property with good radical scavenging ability makes **23** a promising antioxidant drug candidate.

OTHER WATER-SOLUBLE FULLERENES

Tether-directed [3+2] cycloaddition

In 2000, Nakamura and coworkers reported an entirely new water-soluble fullerene (±)-**25** with DNA binding properties.[24] This "two-handed" fullerene, derived from its analog (±)-**26**, is a unique amphiphile possessing a highly hydrophobic C_{60} core for DNA condensation and an S-shaped tetraammonium side chain attached to the core with a *cis*-3 bisaddition pattern for ion pairing with the phosphate backbone of DNA (Figure 5). The synthesis of (±)-**26** used a hexamethylene tether bearing cyclopropenone acetal units at the ends to direct [3+2] cycloaddition (Scheme 6). The structural assignment of the product by NMR spectroscopy and computational analysis indicated that the *cis*-3 addition pattern is most favorable as it has the

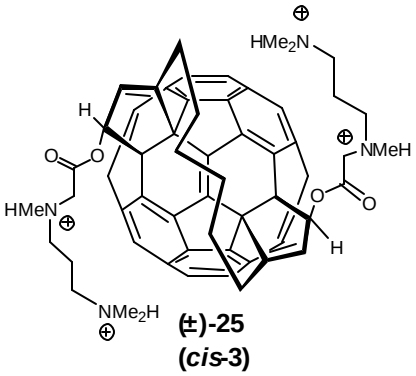
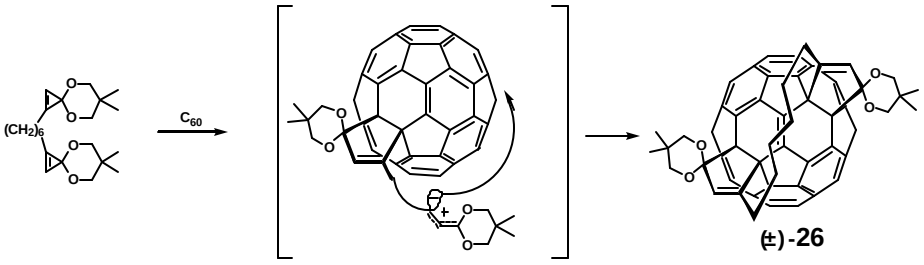


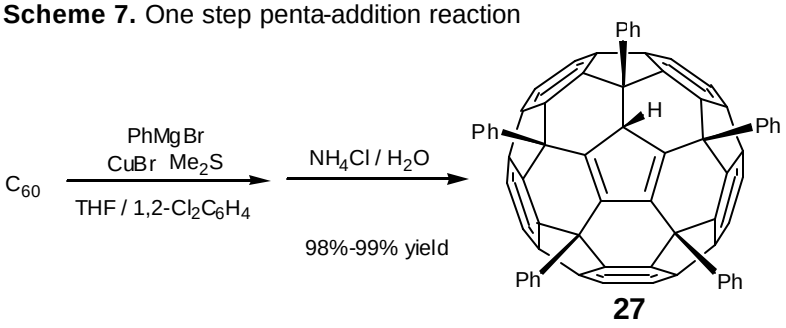
Figure 5. Structure of an amphiphilic tetraammonium fullerene

least comformational strain. Biological studies of fullerene (±)-**25** showed that it reversibly binds to double-helical DNA, and allows delivery of the DNA complex into target cells by phagocytosis. This approach departs from the conventional lipid-mimicking strategy for gene delivery. Further structure-activity investigation of various related compounds lacking some structure features of **25** showed that only **25** exhibited such reversible DNA binding properties, demonstrating the synergy requirement in binding.

Scheme 6. [3+2] cycloadditon of C_{60} with a *cis*-3 pattern



Scheme 7. One step penta-addition reaction



Penta-addition reaction

In 1996, a remarkable one-step five-fold addition of a phenyl copper reagent to C_{60} generated an interesting hydrocarbon $C_{60}Ph_5H$ **27** (Scheme 7).[25] Its anion form $C_{60}Ph_5K$ dissolved freely in water. This method provided a new direction for the synthesis of entirely new bilayer vesicles.[26] Although the mechanism of organocopper reaction remains unclear, Nakamura and coworkers proposed that the reaction proceeded in a sequential addition manner.[27] A series of experimental evidence supported this pathway. In contrast, reactions with Grignard reagents stopped after the first addition. This penta-addition reaction was found to be general for methyl, vinyl, and aryl organocopper reagents and proceeded in quantitative yields. Water-soluble unprotected sugar moieties were also successfully coupled onto this type of fullerene molecules, providing a new tool to study polysaccharide displays.[28]

SUMMARY AND OUTLOOK

Fullerene science has been greatly expanded by tether-directed and templated chemical modifications. With the protocols described, multiple functionalization of fullerenes are simplified. However, a building-block approach is still needed, which is expected to accelerate further development of water-soluble fullerenes. The three water-soluble fullerenes (**23**, **25**, **27**) reported above are being considered for their applications in both medicinal and material science. For instance, the ability of the hexaacid fullerene **23** to trap hydroxyl radicals is being exploited in a treatment of neurodegenerative diseases under investigation by a Canadian company.[8] The

efficacy of the tetraammonium fullerene as an artifical vector for transfection is comparable to that of commercial lipofection reagents.[24] In conclusion, research on the chemical modification of fullerene toward water-soluble derivatives is building a bridge between the worlds of chemical synthesis and biology and materials.

REFERENCES

(1) Kroto, H. W.; Heath, J. R.; O'Brien, S. C.; Curl, R. F.; Smalley, R. E. *Nature*, **1985**, *318*, 162.
(2) Krätschmer, W.; Lamb, L.D.; Fostiropoulos, K.; Huffman, D. R. *Nature*, **1990**, *347*, 354.
(3) Taylor, R.; Walton, D. R. M. *Nature*, **1993**, *363*, 685.
(4) Isaacs, L.; Haldimann, R. F.; Diederich, F. *Angew. Chem. Int. Ed.* **1994**, *33*, 2339.
(5) Friedman, S. H.; DeCamp, D. L.; Sijbesma, R. P.; Srdanov, G.; Wudl, F.; Kenyon, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 6506.
(6) Tokuyama, H.; Yamago, S.; Nakamura, E.; Shiraki, T.; Sugiura, Y. *J. Am. Chem. Soc.* **1993**, *115*, 7918.
(7) Dugan, L. L.; Turetsky, D. M.; Du, C.; Lobner, D.; Wheeler, M.; Almli, C. R.; Shen, C. K.-F.; Luh, T.-Y.; Choi, D. W.; Lin, T.-S. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 9434.
(8) Nakamura, E.; Isobe, H. *Acc. Chem. Res*. **2003**, *36*, 807.
(9) This review is an update of the seminar talk given by Scott A. Long in 1994 with a different focus.
(10) Bingel, C. *Chem. Ber*. **1993**, *126*, 1957.
(11) Hirsch, A.; Camps, X. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1595.
(12) Wang, Y.; Cao, J.; Schuster, D. I.; Wilson, S. R. *Tetrahedron Letters*, **1995**, *36*, 6843.
(13) Hirsch, A.; Lamparth, I.; Karfunkel, H. R. *Angew. Chem. Int. Ed.* **1994**, *33*, 437.
(14) Hirsch, A.; Lamparth, I.; Grosser, T. *J. Am. Chem. Soc.* **1994**, *116*, 9385.
(15) Thilgen, C.; Sergeyev. S.; Diederich, F. *Topics in Current Chemistry*, **2004**, *248*, 1.
(16) Nierengarten, J.-F. *New J. Chem.*, **2004**, *28*, 1177.
(17) Bourgeois, J.-P.; Diederich, F.; Echegoyen, L.; Nierengarten, J.-F. *Helv. Chim. Acta.* **1998**, *81*, 1835.
(18) Bourgeois, J.-P.; Fibbioli, E. M.; Pretsch, E.; Diederich, F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2118.
(19) Bourgeois, J.-P.; Seiler, P.; Fibbioli, M.; Pretsch, E.; Diederich, F.; Echegoyen, L. *Helv. Chim. Acta*. **1999**, *82*, 1572.
(20) Reuther, U.; Brandmüller, T.; Donaubauer, W.; Hampel, F.; Hirsch, A. *Chem. Eur. J.* **2002**, *8*, 2261.
(21) Rapenne, G.; Crassous, J.; Collet, A.; Echegoyen, L.; Diederich, F. *Chem. Commun.* **1999**, 1121.
(22) Lamparth, I.; Hirsch, A. *J. Chem. Soc., Chem. Commun.* **1994**, 1727.
(23) Wang, C.; Tai, L. A.; Lee, D. D.; Kanakamma, P. P.; Shen, C. K.-F.; Luh, T.-Y.; Cheng, C. H.; Hwang, K. C. *J. Med. Chem.* **1999**, *42*, 4614.
(24) Nakamura, E.; Isobe, H.; Tomita, N.; Sawamura, M.; Jinno, S.; Okayama, H. *Angew. Chem. Int. Ed.* **2000**, *39*, 4254.
(25) Sawamura, M.; Iikura, H.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 12850.
(26) Burger, C.; Hao, J.; Ying, Q.; Isobe, H.; Sawamura, M.; Nakamura, E.; Chu, B. *J. Colloid Interface Sci.* **2004**, *275*, 632.
(27) Nakamura, E.; Sawamura, M. *Pure Appl. Chem.* **2001**, *73*, 355.
(28) Isobe, H.; Mashima, H.; Yorimitsu, H.; Nakamura, E. *Org. Lett.* **2003**, *5*, 4461.