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# Templates in Chemistry I

Springer

# Templates in Chemistry I

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**Christoph A. Schalley · Fritz Vögtle · Karl Heinz Dötz**

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## Preface

It is at the same time intriguing from an intellectual point of view and most fruitful with respect to the development of new strategies and applications to transfer concepts from a macroscopic, daily life world to the nanoscopic realm of chemistry. One example is templated synthesis, a term which has been coined by *Daryle H. Busch* in his seminal paper on the synthesis of tetradentate ligands formed around a metal ion through self-condensation of aminobenzaldehyde (*J. Am. Chem. Soc.* 1964, 86, 4834). Since then, the template idea has spread over almost all areas of chemistry ranging from DNA replication to the synthesis of interlocked molecules and to the fabrication of inorganic materials on the basis of organic templates. If a term begins to become “fashionable”, it often loses some of its conceptual power due to exaggerations and misuse. One might argue that this is also true for “template”. Nevertheless, the rapidly increasing number of publications on template effects and templation appearing in any synthesis-relevant journal indicates how important the template strategy in all its facets has become.

The present monograph intends to shed light on a selection of aspects of “template chemistry” by combining chapters from areas as different as templated solid state synthesis, metal-mediated self-assembly processes, organometallic synthesis, the formation of mechanically interlocked molecules, and, last but not least, the production of inorganic materials based on organic templates such as gels. Each chapter has its own scientific focus, although some overlap may exist. We do not consider this a disadvantage, because it provides views from different angles on the same topics. It is obvious that this volume in the Topics in Current Chemistry series cannot be comprehensive at all and follow-up volumes on other aspects of templates in chemistry may be necessary – and are planned – to at least provide a rough overview covering the most important aspects of template chemistry. Based on the rapid development of this area of research, other problems become more and more urgent. One of them is a comprehensive and clear definition of what we should call a template. In view of the many different aspects described by this term, it becomes increasingly difficult to express in a simple, but straightforward way what the concept of templation means, what it does not mean, and how it is related to catalysis. We do not intend to provide a final answer here, but rather like to initiate a discussion in the scientific community about this issue. Such

a discussion may sharpen the language used and, thus, may significantly help to clarify the concepts behind.

Finally, most templates developed in the past have been found by serendipity and empiricism. It would be highly desirable, if this volume contributes a bit to make templates an issue of design and careful planning and in such a way can be implemented into novel synthetic strategies of the future.

Bonn, December 2004

Christoph A. Schalley  
Fritz Vögtle  
Karl Heinz Dötz

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# Spacer-Controlled Multiple Functionalization of Fullerenes

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Dedicated to Professor Fritz Vögtle at the occasion of his 65th birthday

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**Abstract** The chapter provides a survey of the development and applications of the tether- and template-directed regio- and, in the occurrence, stereoselective multifunctionalization of fullerenes over the past ten years. After a presentation of the first tether-directed remote functionalization of C<sub>60</sub>, a broad spectrum of applications is reviewed according to the involved reaction types. The most frequently used chemistry consists of additions of tethered 2-halomalonates (double Bingel reactions) and 1,3-dienes (double Diels-Alder reactions). The former, in particular, were used for the only known tether-directed functionalization of a higher fullerene (C<sub>70</sub>) and also for most of the rare examples of three- and fourfold one-pot tether-directed derivatizations of C<sub>60</sub>. Other, commonly used reactions are [3+2] cycloadditions, notably of azides and, in a few cases, of vinylcarbenes, and azomethine ylides. Some interesting examples of intramolecular [2+2] cycloadditions between fullerene moieties are also included as they are in fact spacer-controlled dimerizations of the carbon spheres. Throughout the account, particular emphasis is put on the diastereoselective generation of chiral fullerene functionalization patterns by use of enantiomerically pure tethers. As compared to tether-directed multiple additions to fullerenes, regioselective functionalizations with non-covalent templates have remained rather rare. Two important examples are reported, one involving a reversible reaction with 9,10-dimethylanthracene in solution, the other one a topochemical anthracene transfer.

**Keywords** Fullerenes · Multiple functionalization · Tether · Spacer · Template · Regioselectivity · Stereoselectivity

#### List of Abbreviations

<i>ap</i>	Antiperiplanar
BET	Back electron transfer
CD	Circular dichroism
CIP	Cahn-Ingold-Prelog
CTV	Cyclotrimeratrylene
CV	Cyclovoltammetry
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DIBAL-H	Diisobutylaluminium hydride
DMA	9,10-Dimethylanthracene
DMAP	4-(Dimethylamino)pyridine
DPV	Differential pulse voltammetry
ESI-MS	Electrospray ionization mass spectrometry
HOBT	1-Hydroxy-1 <i>H</i> -benzotriazole

HOMO	Highest occupied molecular orbital
HSVM	High-speed vibration milling
IUPAC	International Union of Pure and Applied Chemistry
LUMO	Lowest unoccupied molecular orbital
MALDI-TOF	Matrix-assisted laser-desorption ionization time-of-flight
NMR	Nuclear magnetic resonance
ONIOM	Our own <i>n</i> -layered integrated molecular orbital and molecular mechanics method
PET	Photoelectron transfer
PM3	Parametrization method 3
SCF-CI-DV MO	Self-consistent-field configuration-interaction dipole-velocity molecular orbital
SET	Single electron transfer
UV/vis	Ultraviolet/visible

## 1 Introduction

As the chemistry of fullerenes was explored [1–4], it soon became clear that regio- and, in the event, stereoselective multiple functionalization of the spherical carbon polyenes was a key issue to be addressed in order to make pure multiadducts with well-defined addition patterns available on a reasonable scale and without having to resort to tedious purification protocols. Also, a considerable number of interesting addition patterns is not available by simple, consecutive additions due to the intrinsic reactivity of fullerene derivatives [5]. The availability of specific multiadduct regio- and stereoisomers is, however, a *conditio sine qua non* for the full exploitation of the unique three-dimensional fullerene scaffolds and the associated  $\pi$ -chromophores, for example, in advanced materials chemistry [6–11]. In the search for a rational approach to the regioselective formation of multiadducts of  $C_{60}$  and possibly other fullerenes, Diederich and co-workers successfully tried the tether-directed remote functionalization in 1994 [12]. This method had been introduced by Breslow and co-workers to control chemical selectivity in a biomimetic way and it allowed them to carry out reactions at specific positions in steroids and in long alkyl chains [13]. The first step of this approach consists in the attachment to the molecular backbone of an anchor carrying a reactive group at the end of a tether. In the ideal case, conformational preferences of the spacer and steric constraints allow the reactive group to reach and attack only a specific position within the molecular conjugate. Thanks to the remarkable directing effects of many reported tethers in relatively unselective reactions or to their effective competition against the intrinsic reactivity of fullerene derivatives, the spacer-controlled remote functionalization has become the method of choice for selective multiple additions to fullerenes [14–17]. If a tether is solely used as an auxiliary to attain the desired selectivity in a synthesis, its persistence in

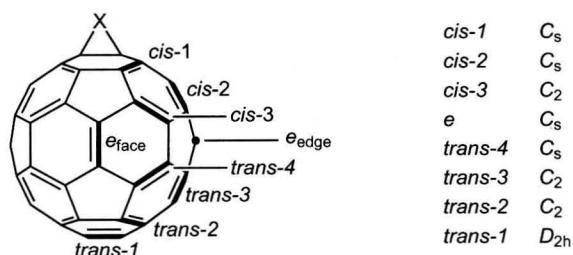
the final product may be unwanted and it should be removable, thus acting as a template [18]. Template-type easy-to-remove tethers have admittedly remained scarce in fullerene chemistry, and further efforts need to be devoted to their development. On the other hand, some non-spacer-based template-directed syntheses have been used with great success in the generation of certain multiaddition patterns of buckminsterfullerene. In combination with other resources such as the exploitation of the intrinsic reactivity of fullerene adducts in further sequential functionalizations or the complete removal of certain addends at a given stage of a synthesis, the templated and spacer-controlled multiple functionalizations have allowed access to a large number of well-defined, multiply functionalized fullerene derivatives over the past decade [14–17].

## 2

### Bisadducts of $C_{60}$ : Addition Patterns and Chirality

Multiple addition to the fullerene sphere can result in the formation of numerous isomeric products. Thus, double, triple, and fourfold addition of symmetrical and identical addends to  $C_{60}$  can afford, in theory, 8, 46, and 262 regioisomers, respectively. The IUPAC has recently presented recommendations for systematic names of fullerenes and fullerene derivatives [19]. However, trivial descriptors, first introduced by Hirsch and co-workers [20], have been widely used for the discussion of the structure of  $C_{60}$ -adducts, since they provide a simple description of regioisomeric bis- and, to some extent, of trisadducts, comparable to *ortho*, *meta*, and *para* in benzene chemistry. The following consideration will be limited to products of double addition of  $C_{2v}$ -symmetric addends across 6-6 bonds (common edge of two six-membered rings) of  $C_{60}$ . According to the system of Hirsch and co-workers, the  $C_{60}$  sphere is divided into three sections with regard to the position of the second addend in reference to the first: the former can lie in the same hemisphere (*cis*), at the borderline between hemispheres (*equatorial* or *e*), or in the opposite hemisphere (*trans*). Within the same hemisphere, there are three sets of four double bonds each (*cis*-1, *cis*-2, and *cis*-3), and there are four different bond types in the opposite hemisphere (*trans*-1 (one bond), *trans*-2, *trans*-3, and *trans*-4 (three sets of four bonds each)) (Fig. 1). If both  $C_{2v}$ -symmetrical addends are identical, the resulting eight possible relative arrangements would give eight possible regioisomeric bisadducts. In case of two different  $C_{2v}$ -symmetrical addends, two different constitutional isomers with *equatorial* addition pattern can arise. Looking from one of the functionalized *e* type bonds to the other, one can see either the edge or the face of a cycle fused to the distal *e* bond. Accordingly, the position of the viewer is described as  $e_{\text{edge}}$  and  $e_{\text{face}}$ , respectively, with regard to the distal *e* bond. The total number of possible regioisomers increases, therefore, to nine.

An interesting aspect of *cis*-3, *trans*-3, and *trans*-2 addition patterns of  $C_{60}$  is their inherent chirality, that is, even addition of two identical addends without chirality elements of their own gives a chiral molecule [21, 22]. Many higher



**Fig. 1** Possible regioisomers for bisadducts of  $C_{60}$ , their trivial designations, and their symmetries in case of identical,  $C_{2v}$ -symmetrical addends

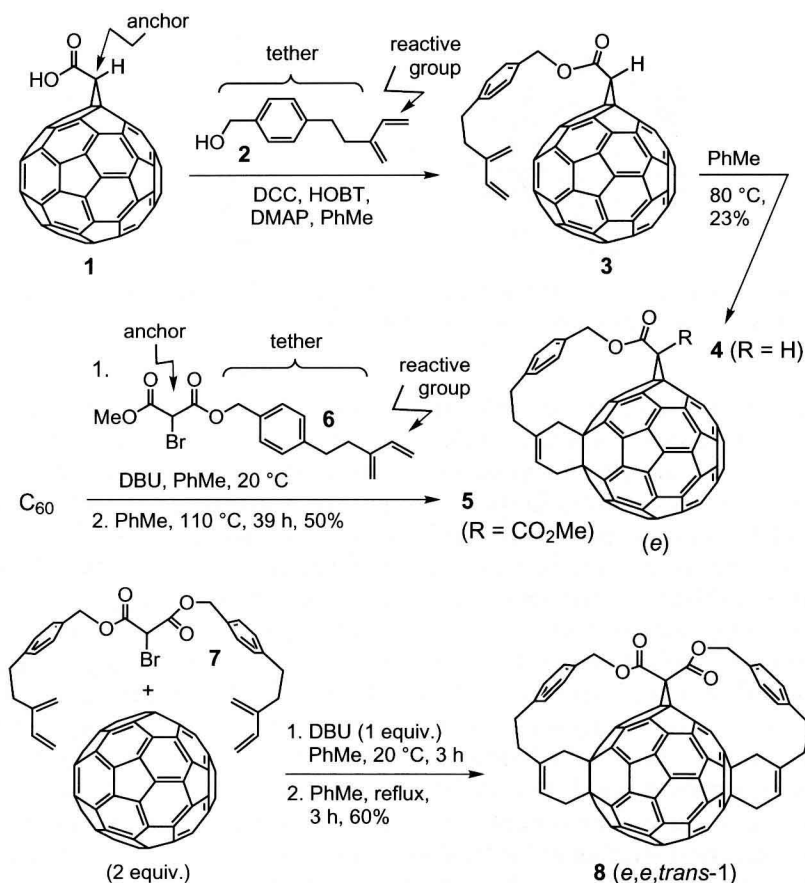
adducts of  $C_{60}$  have also an inherently chiral functionalization pattern, for example,  $C_3$ -symmetrical *e,e,e* or  $D_3$ -symmetrical *trans*-3,*trans*-3,*trans*-3 tris-adducts. There are also fullerene adducts with noninherently chiral addition patterns – their chirality is due to the presence of structurally different addends [21, 22]. Thus, in case of two different addends, *cis*-1, *cis*-2, and *trans*-4 addition patterns become noninherently chiral. The analogy of this situation to that of a center of chirality with tetrahedral coordination should be noted.

The configuration of chiral fullerene addition patterns may in principle be described by indicating the absolute configuration of each stereogenic center on the fullerene surface in terms of the Cahn-Ingold-Prelog (CIP) descriptors (*R*) or (*S*). However, application of this system may be very lengthy and not straightforward due to the highly branched carbon skeleton of fullerene derivatives. Furthermore, as the configuration of individual stereogenic centers in fullerene derivatives cannot generally be inverted independently of the others, the consideration of the fullerene sphere as a single stereogenic unit is advantageous [21, 22], and the configurational descriptors ( $^{f,s}C$ ) and ( $^{f,s}A$ ) (*f*=fullerene, *s*=systematic (numbering), *C*=clockwise, *A*=anticlockwise) were introduced in this context [19, 22]. They relate to the direction of the numbering commencement, i.e., a path traced from C(1) to C(2) to C(3) in a fullerene derivative numbered according to the IUPAC rules [19], taking into account the lowest set of locants for all addends, in particular.

### 3

#### The First Tether-Directed Remote Functionalization of $C_{60}$

In the search for a rational approach toward the regioselective synthesis of multiple adducts of  $C_{60}$  and possibly other fullerenes, Diederich and co-workers initially targeted *e* bisadducts of buckminsterfullerene by the tether-directed remote functionalization [12, 23]. A methanofullerene carboxylic acid group, readily attached to the fullerene core by the Bingel reaction [24], was chosen as an anchor (Scheme 1) and a 1,3-butadiene moiety, known to undergo irreversible Diels-Alder addition to 6-6 bonds of  $C_{60}$  [25, 26], served as reactive



**Scheme 1** The first applications of the tether-directed remote functionalization to fullerene chemistry: regioselective formation of *e* bisadducts **4** and **5**, and of *e,e,trans*-1 trisadduct **8**. DCC=*N,N'*-dicyclohexyl carbodiimide, HOBT=1-hydroxy-1*H*-benzotriazole, DMAP=4-(dimethylamino)pyridine, DBU=1,8-diazabicyclo[5.4.0]undec-7-ene

group to be added to the desired fullerene bond after having been tethered to the anchor. The design of the latter relied on semiempirical PM3 calculations using the relative heats of formation of possible regioisomeric bisadducts as a selection criterion. It was expected that a tether incorporating a (4-methylphenyl)ethane unit (see Scheme 1) should show a high selectivity for the targeted *e*<sub>face</sub> over the neighboring *cis*-3 and *trans*-4, or the alternative *e*<sub>edge</sub> bonds (cf. Fig. 1) [12]. This prediction was supported by more elaborate modeling taking into account the relative populations of potentially reactive conformations of the tether-reactive group conjugate [27].

The tether-reactive group conjugate was attached to the pre-fixed anchor by esterification of wine-red methanofullerenecarboxylic acid **1** with alcohol **2** (Scheme 1) [12]. Subsequent intramolecular reaction of the tethered 1,3-buta-