“Multicomponent Reactions with Fullerenes”

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Supervisor and thesis editor: Prof. Dr. Bernhard Westermann

Declaration

"I declare that I have completed this dissertation without unauthorized help of a second party and only with the assistance acknowledged therein. I have appropriately acknowledged and referenced all text passages that are derived literally from or based on the content of published or unpublished work of other authors."

Bruno Brisolla Ravanello

1. Gutachter: Prof. Dr. Bernhard Westermann

2. Gutachter: Prof. Dr. Marcio Weber Paixão

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To my family and friends

"Somewhere, something incredible is waiting to be known."

Carl Sagan

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Bruno Brisolla Ravanello

Halle (Saale), 2018

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List of abbreviations

Å	Ångström	^{1}H NMR	Proton nuclear magnetic resonance
A	Absorbance	HIV-1	Human immunodeficiency virus
ABDA	9,10-Anthracenediylbis (methylene)dimalonic acid	HMO	Hückel molecular orbital
Bn	Benzyl	HOMO	Highest occupied molecular orbital
Boc	*tert*-Butoxycarbonyl	Hz	Hertz
°C	degrees Celcius (centigrade)	*i*	Iso
C_{60}	Fullerene with 60 carbon atoms	IC_{50}	minimum inhibitory concentration
^{13}C NMR	Carbon nuclear magnetic resonance	I_h	Icosahedral symmetry
calc.	Calculated	IMCR	Isocyanide-based multicomponent reaction
Cbz	Carboxybenzyl	IPR	Isolated pentagon rule
d	Doublet (in NMR)	*j*	Coupling constant
DCTB	*trans*-2-[3-(4-*tert*-Butylphenyl)-2-methyl-2-propenylidene] malononitrile	k	Rate constant
dd	Doublet of doublet (in NMR)	kcal	Kilocalorie
DMAP	4-Dimethylaminopyridine	kV	Kilovolts
DPBF	1,3-Diphenylisobenzofuran	L	Litre
e.g.	Exempli gratia (for example)	LC	Liquid chromatography
equiv.	Equivalent	Ln	Natural logarithm
ESI	Electrospray ionization	LUMO	Lowest unoccupied molecular orbital
FTMS	Fourier transform mass spectrometry	*J*	Coupling constant (in NMR)
FTIR	Fourier-transform infrared spectroscopy	KDa	Kilodalton
Fmoc	Fluorenylmethyloxycarbonyl	M	Molar
g	Gram	m	Multiplet (in NMR)
h	Hour		

MALDI	Matrix-assisted laser desorption/ionization	r.t.	Room temperature
MCR	Multicomponent reaction	RT	Reverse transcriptase
Me	Methyl	s	Singlet (in NMR)
MHz	Megahertz	SOI	Silicon on Insulator
min	Minute	t	Triplet (in NMR)
MS	Mass spectrometry	TFA	Trifluoroacetic acid
Mw	Weight average molecular weight	THF	Tetrahydrofuran
m/z	Mass divided by charge	TLC	Thin layer chromatography
nm	Nanometre	TMS	tetramethylsilane
NMR	Nuclear magnetic resonance	TOF	Time-of-flight mass spectrometer
o	Ortho	tt	Triplet of triplets (In NMR)
$^1O_2$	Singlet oxygen	UV	Ultraviolet
p.	Page	U-4CR	Ugi Four-component reaction
p	Para	VIS	Visible
P-3CR	Passerini three-component reaction	w/v	Weight divided by volume
PCBM	[6,6]-phenyl-C_{61}-butyric acid methyl ester	°	Degree
PDT	Photodynamic therapy	π	Pi
PEG	Polyethylene glycol	α	Alfa
PS	Photosensitizer	δ	Sigma
ppm	Parts per million	μ	Micro
R^2	Coefficient of determination	%	Percentage
ROS	Reactive oxygen species	Φ_Δ	Quantum yield

Chapter 1

Fullerenes principles and their role in isocyanide-based multicomponent reactions

Abstract

The curious carbon cage structure of fullerenes, coupled with their unique chemical, physical and biological properties makes this class of compound valued assets in many research areas. To supply the demand of novel derivatives, just a few classical reactions offer products with good yields under mild conditions. Multicomponent reactions on the other hand, can add the desired diversity in the synthesis of fullerene derivatives, presenting an alternative pathway and boosting its applications in material and medical science. Therefore, the aim of this chapter is to provide an overview on fullerenes, multicomponent reactions and relevant topics.

1.1 Nanotechnology

By definition, nanotechnology is the branch of technology that deals with dimensions and tolerances of less than 100 nanometres (nm), especially the manipulation of individual atoms and molecules.[1] It all started in 1959 with an ambitious talk from Richard P. Feynman at the American Physical Society meeting at Caltech titled "There's plenty of room at the bottom".[2] Feynman, who later won a Nobel Prize in physics (1965), challenged his peers to pursue studies and manipulations of matter on a molecular level. Although this inspiring talk, it took further fifteen years for the first scientific report to include the word "nanotechnology" in its title, in 1974 by Tanigushi and co-workers, opening a new chapter in science.[3]

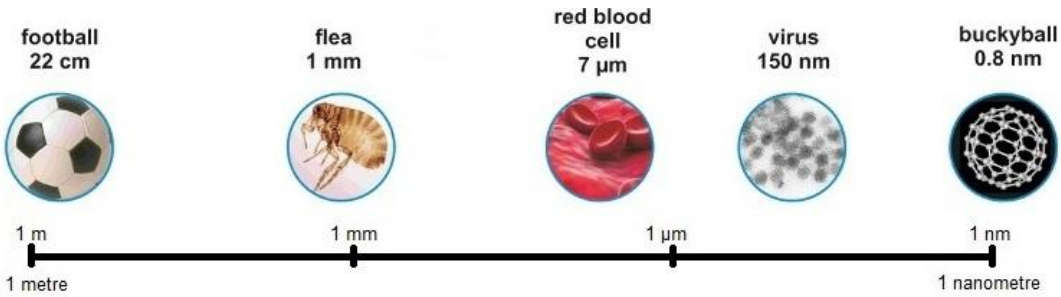


Figure 1. Scale of relative dimension of various objects.

When materials and molecules are in the 1 - 100 nm range they are governed by quantum mechanics, the branch of physics responsible to understand phenomena in nanoscale. In quantum mechanics, atoms and molecules behave differently than in larger molecular systems (classical physics), revealing unique properties, effects and possibilities to be explored by chemists, physicists, biologists and engineers.[4-10]

Today, nanomaterials are present in our everyday life including, but not limited to: cosmetics, where nanosomes are used to transport active ingredients into the skin's outer layer; sunscreens, containing nanosized particles of titanium dioxide that reflect ultraviolet (UV) radiation; deodorants, with silver nanoparticles that act as anti-bactericide and electronics and computers, where IBM uses 90 nanometer Silicon on Insulator (SOI) technology to reduce heat and improve performance.[11] Among the many nanomaterials studied nowadays, fullerenes have a leading role in the development in this field, being already used in some high end applications and with multiple possibilities.[12-16]

1.2 Fullerenes

Fullerenes were discovered in 1985 by H. W. Kroto, R. E. Smalley and R. F. Curl who in 1996 were awarded the Nobel Prize in chemistry for their work. When conducting experiments with a laser-vaporization supersonic cluster beam, and after the vaporization of graphite from the disk, Kroto and co-workers found in their mass spectrometer data a dominating signal at m/z = 720. After long discussions and literature consults they concluded that a spontaneous formation of spherical clusters of hexagons and pentagons with predominantly 60 carbons atoms occurred.[17] By the similarity of its structure with the geodesic domes of the architect R. Buckminster Fuller, the authors named this molecule *Buckminsterfullerenes*.

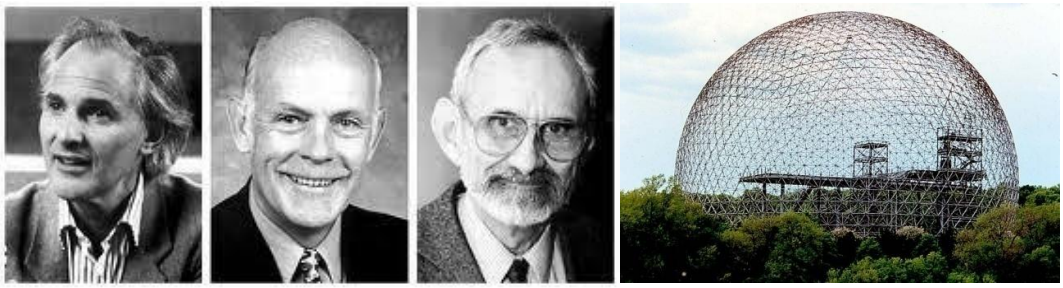


Figure 2. H. W. Kroto, R. E. Smalley and R. F. Curl and the geodesic dome of R. Buckminster Fuller.

Up until then, only two elemental carbon allotropes were known, graphite and diamond, one very distinct from the other, with two and three dimensional networks of undefined atoms, and with different practical applications.[18] Upon their discovery, fullerenes became the third known form of carbon allotropes and the first with a defined three dimensional structure, attracting attention of the scientific community (Figure 3).[19,20]

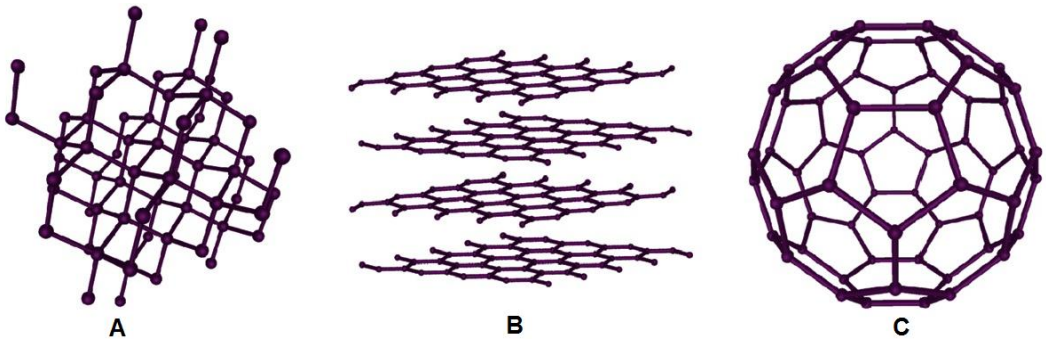


Figure 3. Structure of (a) diamond, (b) graphite, and (c) fullerene C_{60}.

Fullerenes are spherical, hollow nanomolecules, of fused pentagons and hexagons, with the stoichiometry C_{20+2n}. Most stable allotropes follow *Euler's theorem* and the *isolated pentagon rule* (IPR). *Euler's theorem* states that to close a sphere with *n* hexagons, twelve pentagons are necessary. In parallel, the IPR predicts that only fullerenes with all twelve pentagons isolated by hexagons should form stable structures, due to the steric strain that neighbouring five member rings will cause.[21-23]

Connecting these two rules, the fullerene with 60 carbon atoms (C_{60}) appears as the smaller fullerene that respect the *isolated pentagon rule*, explaining its stability and the higher presence in Kroto's initial experiments (Figure 4).

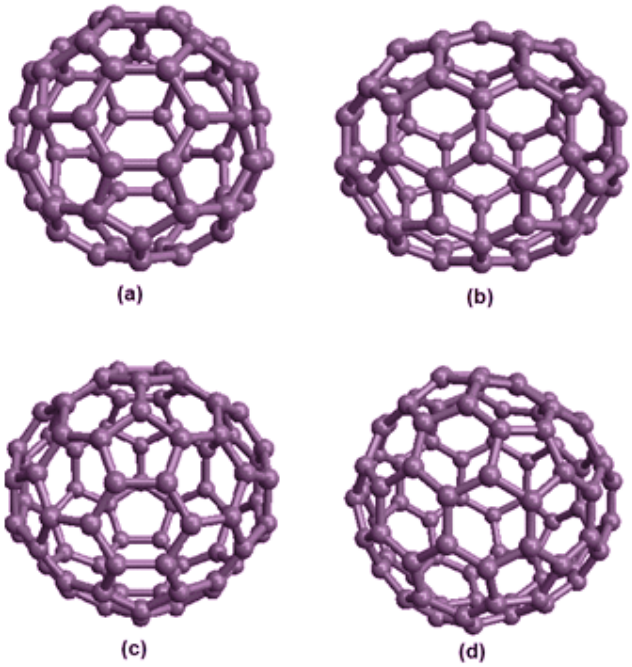


Figure 4. Fullerenes (a) C_{60}, (b) C_{70}, (c) C_{78}, and (d) C_{84}.

1.2.1 Fullerene C_{60}

Consisting of twelve pentagons and 20 hexagons (I_h symmetry), fullerene C_{60}, also known as Buckyball (due to the resemblance to a football), is the best known representative of its class. All the carbon atoms in the structure are equivalent, indicated by the presence of only one signal at 143.2 ppm in the ^{13}C NMR spectrum for pure C_{60} in deuterated benzene.[24]

Due to its curved surface, the orbitals of the carbon atoms of C_{60} are not parallel to each other, causing a high strain energy which is equally distributed among all 60

atoms.[25-27] Another effect of the fullerene curvature is the increased *p*-character of the hybrid orbital sp^x, from sp^2 (usual to planar aromatic systems) to $sp^{2,278}$. This change, connected with the low overlapping of the atomic orbital, causes a shift in the reactivity of C_{60} when compared to planar conjugated systems of the same size, increasing significantly fullerene C_{60} electron affinity.[28,29]

As a result of the presence of both five and six member rings there are two types of bonds in C_{60} structure (Figure 5). The [6,6] bonds are located in the junction of two hexagons, have a length of 1.38 Å and a higher double-bond similarity. The [5,6] bonds are located at the pentagon-hexagon junction, have a length of 1.45 Å and a higher single-bond similarity. Because of this bond alternated structure and the strong electron affinity, fullerene C_{60} is not considered an aromatic compound but an electron deficient polyolefin.[30]

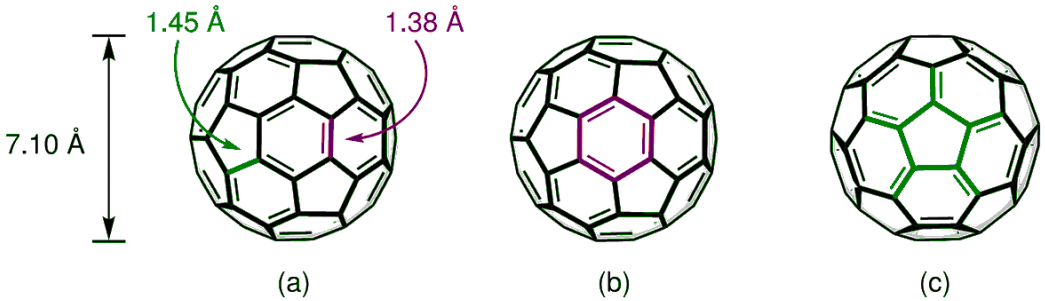


Figure 5. Illustration of (a) [6,6] and [6,5] bonds and (b) (c) preferred position of double bonds.

After their discovery in 1985 by Kroto and co-workers, several properties and reactions of C_{60} could be predicted, but only in the next decade, after the development of more sophisticated production methods, this compound was available in meaningful quantities to be studied comprehensively. One of these methods, developed by Krätschmer and Huffman in 1990, was the arc vaporization of two graphite rods under helium atmosphere and high pressure.[31] Since then, additional production methods were developed and refined (e.g., induction heating of graphite, solar furnaces, pyrolysis of naphthalene), allowing the in-depth investigation of fullerenes features.[32-35]

1.2.2 Physical properties

The unique structural characteristics of these carbon allotropes strongly affect their physical properties and reactivities. The first chemicals transformations aimed to explore their redox potential and fullerene C_{60} revealed to be highly electronegative,

being able to tolerate numerous reduction steps. In one of the first studies (1992), Echegoyen and co-workers accomplished the reversible reduction of fullerene C_{60} to the hexaanion C_{60}^{6-} under optimized reaction conditions.[36] On the contrary, the monocation C_{60}^{+} could only be obtained under harsh conditions, as expected from an electron deficient molecule.[37,38] Looking at the *Hückel molecular orbital* diagram (HMO) of C_{60} (Figure 6) the differences above can be explained. Theoretical calculations indicate that the highest occupied molecular orbital HOMO (h_u) is five-fold degenerated, while the lowest unoccupied molecular orbitals LUMO (t_{1u}) and LUMO+1 (t_{1g}) are triply degenerated and relatively low in energy.[39,40]

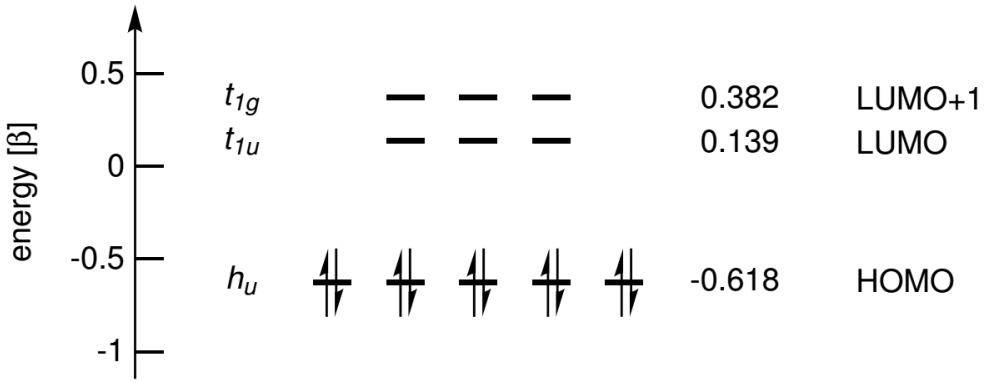


Figure 6. *Hückel molecular orbital* diagram of C_{60}.

Fullerene C_{60} also has a distinct affinity towards radicals, creating stable diamagnetic and paramagnetic products.[41] In virtue of this and their high electronegativity, fullerenes are powerful radical scavengers, having remarkable anti-oxidant character.[42] Some noteworthy features include their low reorganization energy (caused by their highly stiff structure), their ability to form superconducting species when combined with some alkali metals, the fact that they possess non linear optic properties and are able to maintain a long duration triplet state.[7,8,43,44]

Like previously mentioned, one of the main characteristics of fullerene C_{60} is its immense ring strain. As a result of the presence of rigid fused five membered rings, single bonds pairs have angles of 108° compared to the normal bond angle of 120°. A great amount of strain can be alleviated by rehybridization of the atoms when compounds are added to the fullerene structure, turning them susceptible to a large number of addition and cyclopropanation reactions. The high-reducibility of fullerenes combined with all their unique characteristics, make them especially attractive building blocks not only for chemists but also in the field of physics, biology, engineering, computational chemistry, and medical science.[29]

1.2.3 Solubility

The main factor restraining the broader use of fullerenes in further applications is the very low solubility of these compounds in most organic solvents (Table 1). Since they are apolar molecules and hardly polarizable (large HOMO-LUMO energy gap), their interaction with solvent molecules is very weak, especially in water and polar solvents, limiting medical and biological applications. In addition, fullerene C_{60} aggregates easily, lowering its solubility even more.[45] Higher solubility values are observed for aromatic solvents and carbon disulfide, being these the solvents of choice for most purposes. To overcome such barriers, researchers have focussed their efforts in derivatizing fullerenes to enhance their solubility, modify physical and chemical attributes and tailor desired features.[46]

Table 1. C_{60} solubility in most common organic solvents.

Solvent	C_{60} Solubility (mg/mL)	Boiling Point (°C)
n-Hexane	0.043	68
Dichloromethane	0.26	39.6
Chloroform	0.16	61.2
Methanol	0.0001	64.7
Toluene	2.8	110.6
Tetralin	16	207
Chlorobenzene	7.0	131
1,2-Dichlorobenzene	27	180.5
Carbon disulfide	7.9	46.3

1.2.4 Reactivity

In agreement with the physical and structural properties already mentioned, fullerene C_{60} reactivity is influenced by a few general principles:[29]

- The curved structure of C_{60} causes pyramidalization of the atoms and accounts for the pronounced strain energy. Reactions that lead to sp^3 carbon atoms can relief some of the strain and are highly favoured.

- The low degenerate LUMO orbital and the incomplete filling of the π orbital, which also have a pronounced *s* character, make C_{60} similar to an electron deficient polyolefin, having a high electron affinity, allowing reductions and nucleophilic attacks.

- The rigid and curved design of C_{60}, allied with the pyramidalized atoms emulates an inert interior, being able to "trap" many species inside.

- The regioselectivity of all addition reactions is ruled by the minimization of energetically unfavorable [5,6] double bonds in the C_{60} cage. Hence, addition reactions usually occur at the [6,6] bonds.

1.2.4.1 Fullerene C_{60} reactions

After the advances in production methods, fullerenes have been employed in abundant transformations, giving access to a large number of diverse fullerene derivatives. These many reactions can be divided in five main classes (Figure 7):

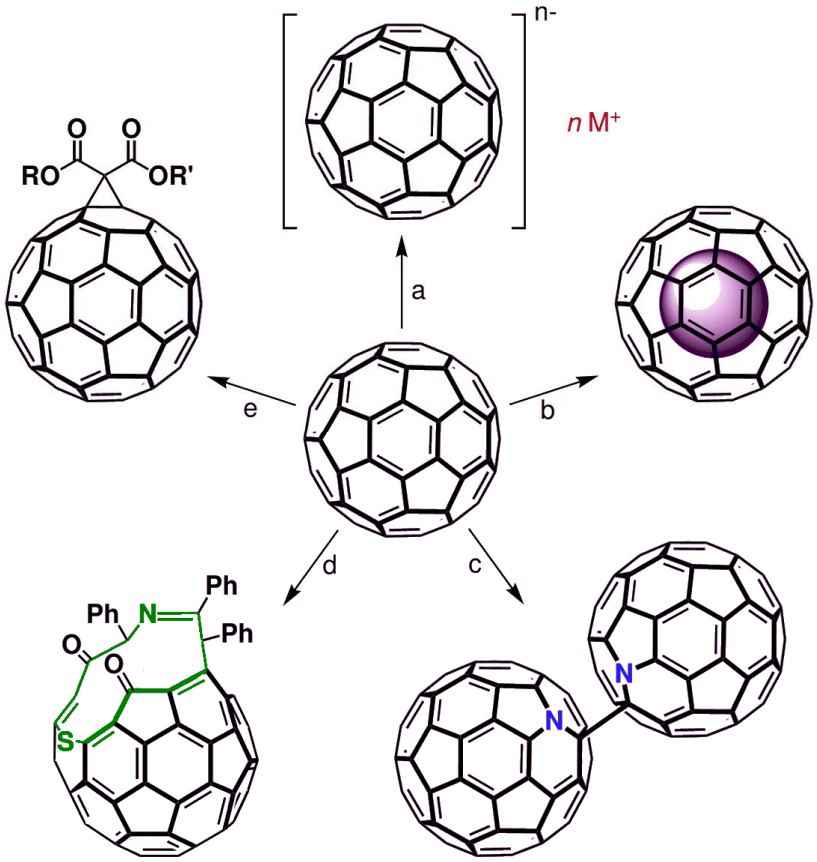


Figure 7. Classes of fullerene reactions: (a) Metal fullerides, (b) endohedral functionalizations, (c) heterofulleres, (d) ring opening reactions, and (e) exohedral functionalizations.

a) Reaction with alkali or alkaline earth metals, yielding metallic salts like K_3C_{60} with appealing superconductive properties.[38,47-50]

b) Encapsulation of small guest molecules to form inclusion complexes of C_{60} with metals or noble gases. Studies show that even nitrogen atoms could be incorporated inside the cage to assist in spectroscopic analysis of such species, including $N@C_{60}$, a material of great scientific interest, and extremely high commercial value.[51-54]

c) Formation of heterofullerenes by replacing one or more carbon atoms from the structure. Many clusters including varied numbers of boron, nitrogen, oxygen, silicon, phosphorus, iron, copper, among other metal atoms could be theoretically predicted, detected by mass analysis and in some cases isolated.[55-60]

d) Ring opening and fragmentation reactions, which can be precursors for endohedral fullerenes, e.g., the elegant inclusion of a H_2 molecule inside the fullerene cage.[61-63]

e) Exohedral functionalization of C_{60} by addition reactions. Regarded as the most important type of chemical transformation for fullerenes, this process has been explored and perfected during the last decades with an extensive variety of synthesized derivatives by means of nucleophilic additions of Grignard reagents,[64] organolithium compounds,[65] amines,[66,67] cyanides,[68] oxygenation,[69] halogenation,[70] hydrogenation,[71] Diels-Alder reactions,[72] Prato cycloaddition[73] and Bingel cyclopropanation,[74] where the Prato and Bingel transformations can be highlighted as key reactions in fullerene chemistry.[29]

Although various methods are available for the synthesis of C_{60} adducts, with the continuous growth of nanotechnology and the expansion of fullerene applications, new synthetic procedures are fundamental to supply researchers with the necessary tools to develop novel and more complex compounds.

1.2.4.2 Multiaddition reactions

After the first addition reaction to the C_{60} structure, eight positions are available for a subsequent [6,6] bond attack (Figure 8), yielding eight distinct regioisomers with similar polarity and very difficult separation process.

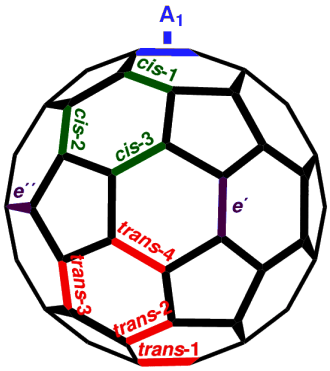


Figure 8. Possible bis-addtion products.

Since geometry plays a major role into the derivatives properties, the regioselective synthesis of bis-adducts has great importance.[29] The use of different procedures and starting materials can shift the regioisomers ratios, granting some selectivity to the process. One breakthrough in this area was accomplished by Diederich and co-workers (Figure 9), by means of tether-directed bis-functionalization, to achieve the selective formation of the desired bis-adduct.[75]

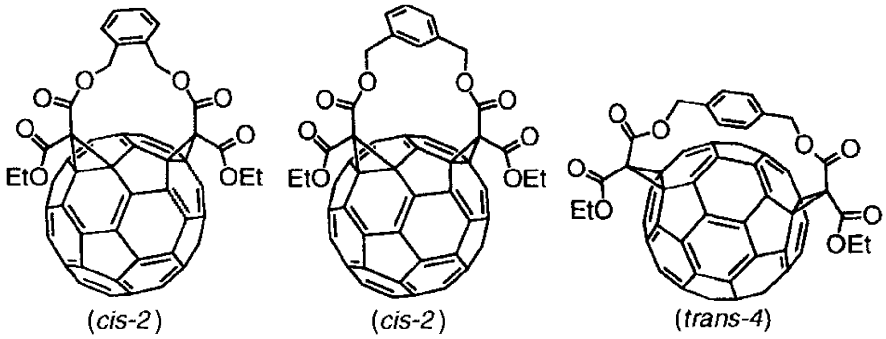


Figure 9. Diederich synthesis of bis-functionalized fullerenes.[75]

1.2.5 Applications

Extensive research on the application of fullerenes has been conducted since their discovery and now, after 30 years, many of the previously predicted applications have been confirmed, along with some new and exciting prospects.[76,77]

1.2.5.1 Material science applications

Fullerene derivatives, like their predecessor, are semiconducting materials in which the electrons are charge carriers. They inherit such properties due to the π conjugation of the carbon structure.[78,79] Frequently, the mobility of electrons in thin films of C_{60} derivatives is much lower than for C_{60}, but in complex systems of fullerene derivatives and polymers, this value can be magnified.[80-82] Derivatives like [6,6]-phenyl-C_{61}-butyric acid methyl ester (PCBM) have been applied for the manufacture of semiconductors together with organic polymers (Figure 10), showing promising qualities.[83] Fullerenols derivatives (Figure 10) can also function as proton conductivity materials, with proton conductivity values much larger than their electronic conductivity.[84]

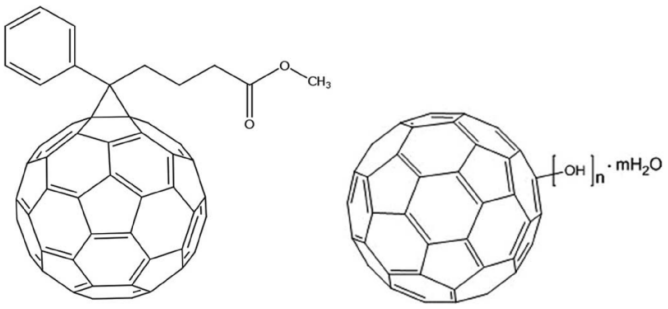


Figure 10. The structure of [6,6]-phenyl-C_{61}-butyric acid methyl ester and fullerenols, respectively.[76]

The mechanical properties of a polymer-fullerene composite can notably change in comparison to the polymer precursor. The addition of PCBM to a polymer matrix improves the mechanical moduli.[85,86] PCBM also increases the mechanical elasticity of semiconducting polymers for solar cells without affecting the photovoltaic properties, while also increasing interlayer adhesion.[87,88]

1.2.5.2 Antioxidant activity

Due to their high affinity towards electrons and radicals, fullerenes are excellent antioxidants, being classified as "radical sponges".[89] The main class of derivatives evaluated as antioxidants are fullerenols ($C_{60}(OH)_n$), where *n* can correspond up to 44 hydroxyl groups. Studies showed strong antioxidant properties of these compounds, changing the cellular redox state and, therefore, proposed this derivative as a cytoprotective agent.[90] Grebowski and co-workers measured the rate constants of hydroxylated fullerene $C_{60}(OH)_{36}$ interacting with hydroxyl radicals ($^{\bullet}OH$) and verified similar values to $C_{60}(OH)_{18}$, indicating that the decreased number of π bonds did not affect the rate constant for this reaction.[91,92]

Unfunctionalized fullerene C_{60} is also currently used in commercial cosmetics creams for its antioxidant properties. Recent clinical trials have shown that a gel formula of C_{60} can be successfully used in the treatment of *acne vulgaris*, an inflammatory disease linked with oxidative stress.[93]

1.2.5.3 Antiviral activity

The surge of multidrug resistant viruses and bacteria remains a serious issue in our time, thus the development of novel types of structurally distinct drugs is a critical need and, with their unique design, fullerenes can accomplish this goal. Recently, Khakina and co-workers reported a fullerene derivative (Figure 11a) that exhibits low cytotoxicity and stops the HIV-1 infection *in vitro*, with a minimum inhibitory concentration (IC_{50}) of 4.6 μM.[94] Yasuno and co-workers synthesized pyridine/pyridinium-type fullerene derivatives (Figure 11b), which inhibit the HIV-1 reverse transcriptase (RT) in a cell-free environment without cytotoxicity, proving the important role of the fullerene cage for the inhibition of HIV-RT.[95]

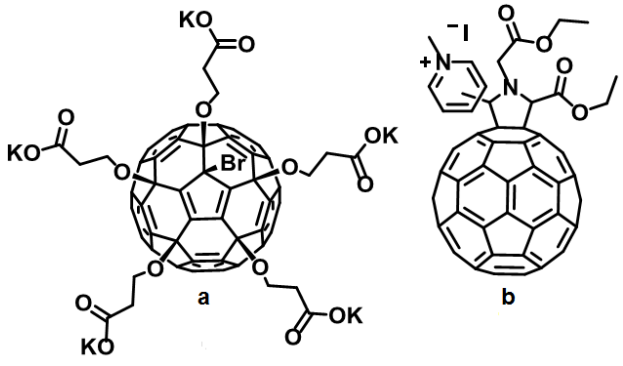


Figure 11. Structure of anti HIV-1 fullerene derivatives.[94,95]

In 2016 Muñoz and co-workers published the synthesis of dendritic glycofullerenes. With up to 120 glycosides (Figure 12), these fullereno dendrimers showed very potent antiviral activity against the Ebola virus, in the range of nM and pM concentrations.[96]

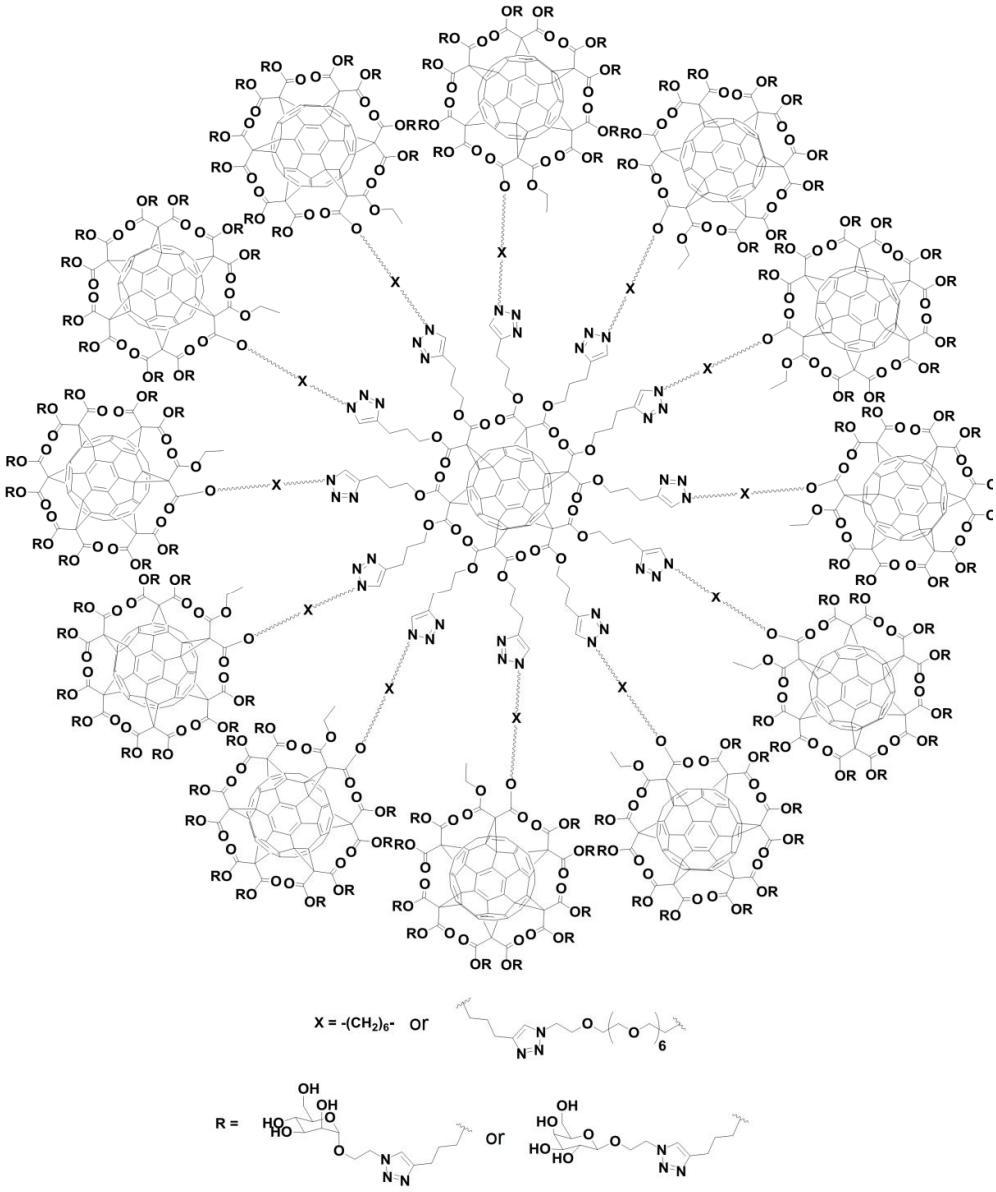


Figure 12. Dendritic glycofullerenes by Muñoz and co-workers. [96]

1.2.5.4 Photodynamic activity

Photodynamic therapy (PDT) is a clinically approved therapeutic method for the treatment of many medical conditions, especially cancer.[97] It is based on the photoexcitation of a biocompatible photosensitizer (PS) at a wavelength that matches the absorption of the PS, causing the local generation of cytotoxic reactive oxygen species (ROS). ROS create oxidative stress that damage cells constituents leading to the death of tumor cells.[98] Considering that the PS is only active after irradiation, PDT has striking selectivity and causes less side effects when compared to traditional anticancer therapies.[99]

There are two possible mechanisms of action for most PS (Figure 13). In type I, an electron transfer of the excited PS and a biomolecule (represented by **X**) present in the media produces free radicals and radical ions, which reacts with molecular oxygen to generate ROS such as peroxide, superoxide and hydroxyl radicals. In a type II mechanism, an energy transfer of the excited PS and molecular oxygen produces singlet oxygen ($^1O_2$), a unique type of ROS. In general both mechanisms happen simultaneously, but with different ratios based on the type of substrate, oxygen concentration and the distance of the photosensitizer to the substrate.[100,101]

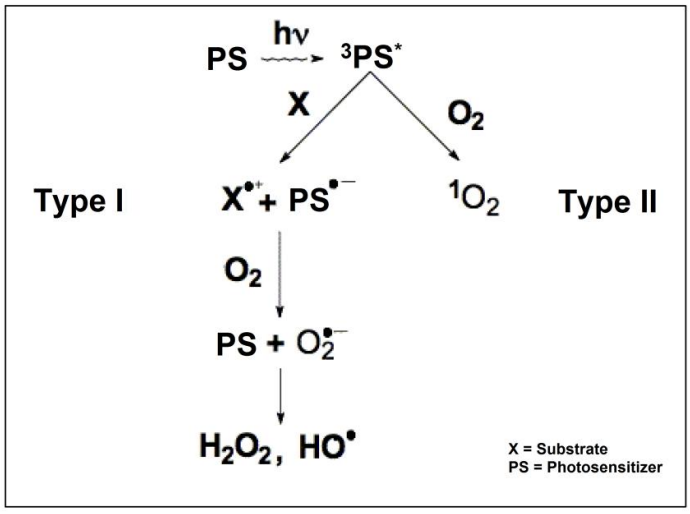


Figure 13. General mechanism of the action of a photosensitizer.

After irradiation, fullerene C_{60} is excited to a triplet state that after decay, converts molecular oxygen to singlet oxygen, meaning it mostly follows a type II mechanism. Singlet oxygen, unlike common radicals, cannot interconvert to other reactive oxygen species. It also has a very low half-life compared to regular ROS,

returning rapidly to the fundamental state through energy transfer to the solvent in the media.[102,103] By calculating its half-life in water, is possible to estimate that the distance $^1O_2$ can diffuse in the cell before returning to its fundamental state is 270 nm. This very short distance means that $^1O_2$ only damages the regions where the photoexcitation occurred, minimizing the death of healthy cells during the process, therefore reducing side effects.[104]

The derivatization of fullerene C_{60} with *n*-butyl sulfonic acid salts by Yu and co-workers showed high efficiency in singlet oxygen generation, explained by the low barrier intermolecular energy transfer from the PS to molecular oxygen.[105] Franskevych and co-workers commented on the cytotoxic effect of C_{60} when irradiated with visible light on leukemic L1210 cell lines. Their studies indicate that PDT treatment is a great option for restoration of drug-resistant leukemic cell sensitivity to induction of mitochondrial way of apoptosis.[106]

Fullerene C_{60} derivatives, synthesized by Ikeda and co-workers (Figure 14), were added into liposomes and under the same conditions, the photodynamic activity of the compound with a quaternary ammonium salt was much larger than the other two compounds, result attributed to a more effective generation of singlet oxygen, as evaluated by the use of 9,10-anthracenediylbis(methylene)dimalonic acid (ABDA) as detector.[107,108]

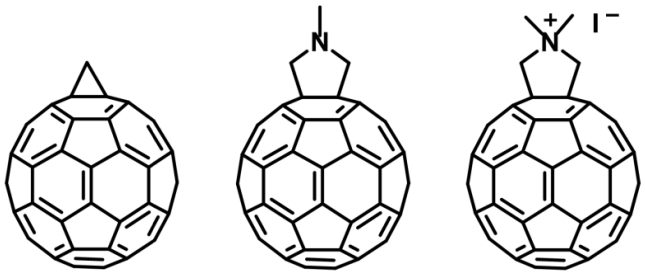


Figure 14. C_{60} derivatives evaluated for their photodynamic activity.[107]

1.3 Multicomponent reactions

Multicomponent reactions (MCRs) are processes that connect three or more molecules through a single transformation (Figure 15), leading to high structural diversity and molecular complexity. Currently, they are at the forefront in the search for the ideal synthesis, fulfilling most of the required qualities (simple, one pot process, high yields, high atom economy, readily available starting materials and environmental friendly).[109,110] Due to the high diversity of their products, they are a powerful tool in the

pursuit of new pharmacologically active structures. Extensive libraries of compounds can be synthesized employing a variety of components, facilitating the rapid screening for new types of drugs, an ever increasing necessity nowadays with the fast development of drug resistant bacteria.[111]

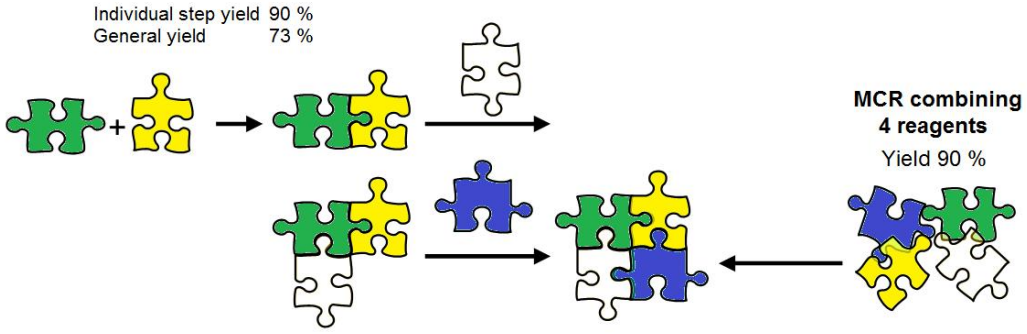
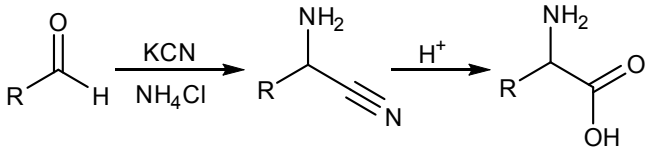


Figure 15. Illustrative example of a multicomponent reaction.

In the beginning of their development, most MCRs were based on classical condensations between carbonyl compounds and numerous nucleophiles, where it can be highlighted the first known MCR, the Strecker synthesis of amino acids from aldehydes, potassium cyanide and ammonium chloride, reported in 1850 (Scheme 1).[112]

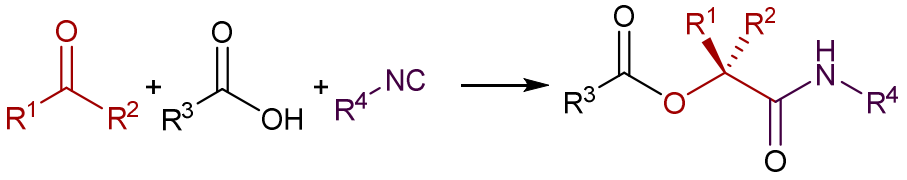


Scheme 1. Strecker synthesis of amino acids.

Later, with more accessible protocols for the synthesis of isocyanides, a new class of MCR emerged, named isocyanide-based multicomponent reactions (IMCR).[110,111] IMCRs explore the ambiphilic character of isocyanides, an unusual trait that allow them to act both as nucleophile and electrophile.[113] The two most successful examples of IMCRs are the Passerini three-component reaction (P-3CR) and the Ugi four-component reaction (U-4CR), which uppon their discovery expanded considerably the types of transformations that can be achieved.

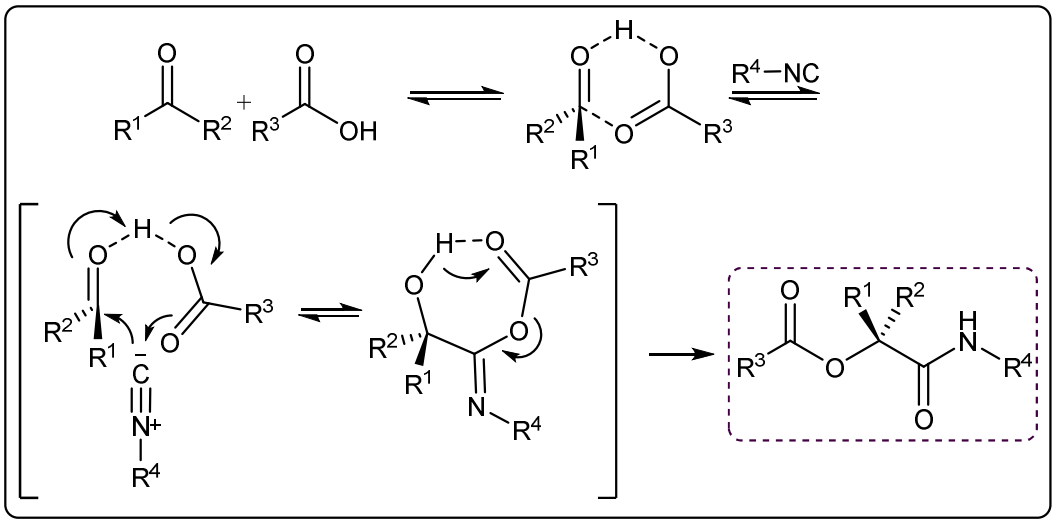
1.3.1 Passerini three-component reaction

This multicomponent reaction of a carbonyl compound, a carboxylic acid and an isocyanide was discovered in 1921 by Mario Passerini and is considered the oldest isocyanide-based MCR (Scheme 2). The Passerini reaction yields α-acyloxy amides (depsipeptides) and simultaneously introduces three diversity points under mild conditions and with high atom economy.[114,115]



Scheme 2. Passerini three-component reaction

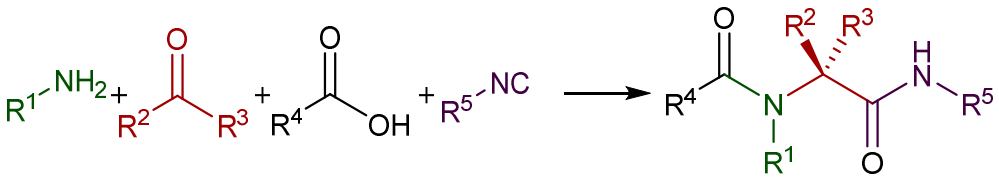
Although many reaction mechanisms have been proposed during the years, the most generally accepted one is shown in Scheme 3. In this hypothesis, the hydrogen-bonded cluster formed by interaction of the carboxylic acid and the carbonyl component reacts with the isocyanide in a concerted way to give the primary α-addition intermediate, through a relatively nonpolar cyclic transition state. In the final step, the α-addition adduct rearranges to form the stable Passerini product, with the mechanism being in agreement with the observed faster reaction time in apolar solvents.[116]



Scheme 3. Mechanism of the P-3CR.

1.3.2 Ugi four-component reaction

Since the first report in 1959 by Ivar Ugi, this reaction of an aldehyde/ketone, an amine, a carboxylic acid and an isocyanide has become the hallmark of MCRs, yielding a peptoid-like backbone, present not only in peptides but also in alkaloids and heterocycles of biological relevance (Scheme 4).[117,118]



Scheme 4. Ugi four-component reaction.

The Ugi reaction also boosted the combinatorial and parallel synthesis fields, where its wide substrate scope and ideal synthesis aspects can be used to rapidly, and more important predictably, combine four building blocks.[119] Beyond its value in combinatorial, peptidic and medicinal chemistry, the Ugi reaction is considered environmentally friendly, being performed in almost any solvent, without the need of special reaction conditions and having water as the sole by-product.[120]

Currently, almost 60 years after its discovery, many variants of the Ugi reaction have been reported, where the classical components can be replaced by compounds with similar reactivity. Hydrazoic acid, cyanates, thiocyanates, water, salts of secondary amine, hydrogen sulfide, and hydrogen selenide have all been used as alternative to the acid component. In a similar way, any building block having an adequate nucleophilic NH group can be used, such as ammonia, primary and secondary amines, hydrazines, diaziridines and hydroxylamines. With such a wide substrate scope, different and highly versatile scaffolds can be originated as depicted in Figure 16.[109,113,121,122]

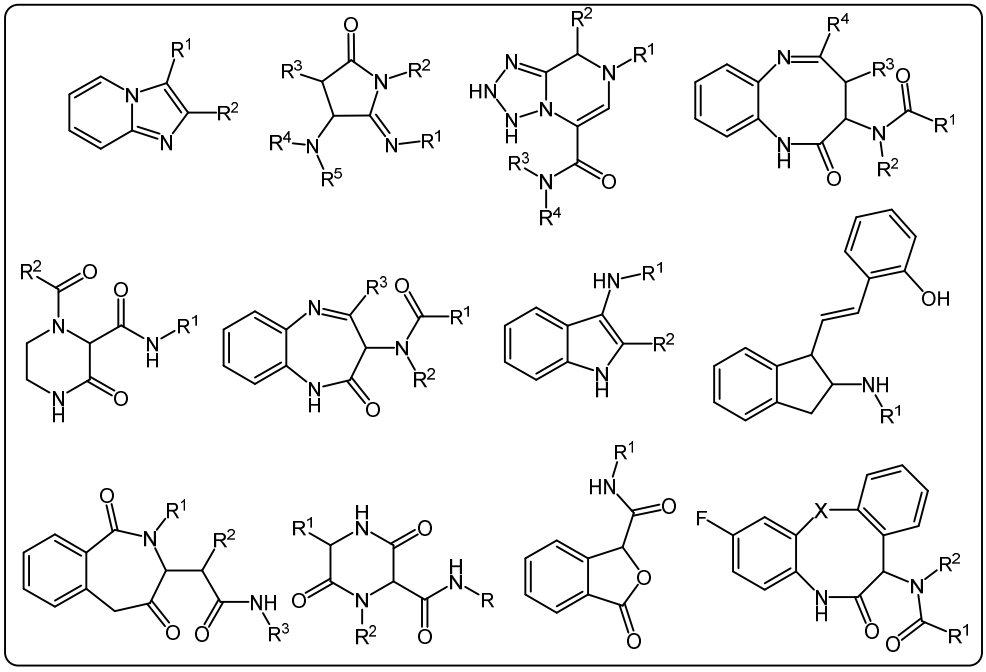
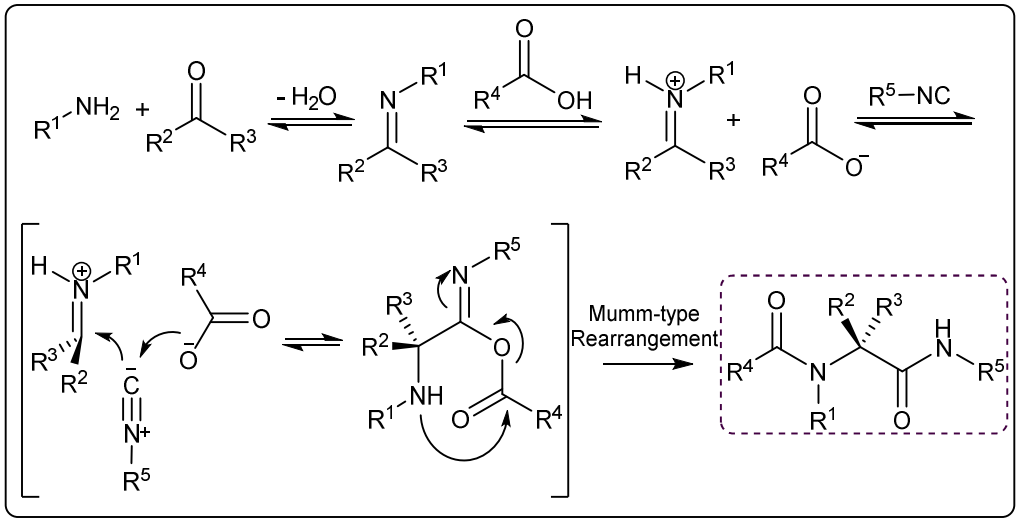


Figure 16. Examples of possible Ugi product scaffolds.

The most accepted mechanism of the Ugi reaction (Scheme 5) starts with the condensation of the amino and aldehyde components to form the imine (Schiff base). Next, the acid component protonates the nitrogen atom of the Schiff base, activating it and increasing the electrophilicity of the carbon-nitrogen double bond. The iminium ion and acid anion add to the isocyanide carbon atom, giving the intermediate (α-product). The final and irreversible step is an intramolecular acylation followed by rearrangement (Mumm-type rearrangement) to yield the Ugi product.[120,122]



Scheme 5. Mechanism of the U-4CR.

1.4 General goals

With all of the above in consideration, the general goals of this PhD thesis are:

- Investigate a methodology to decorate fullerene C_{60} *via* the Passerini reaction and Ugi reaction;
- Expand the scope of the synthesized products by using bifunctional anilines which allow further derivatization;
- Develop a new multicomponent reaction involving fullerene C_{60}, *N*-protected amino acids and isocyanides.

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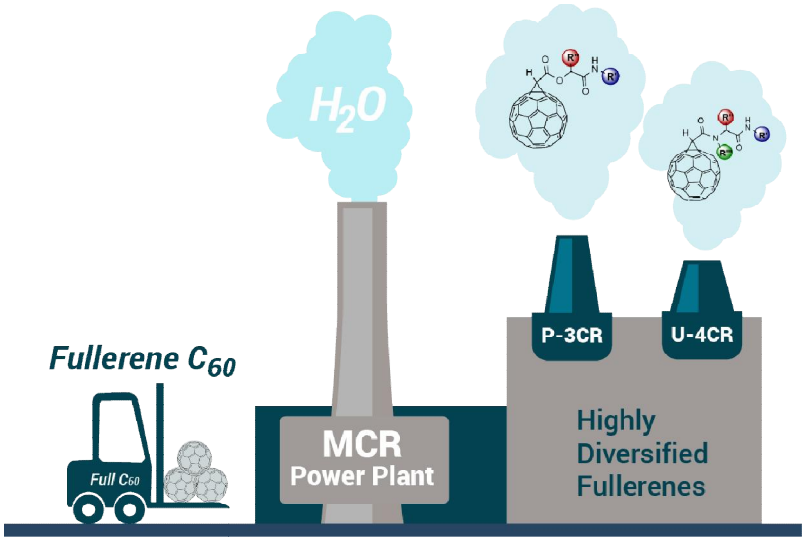
Chapter 2

Diversity driven decoration and ligation of fullerene by Ugi and Passerini multicomponent reactions

Abstract*



Looking to provide an efficient and versatile method for the diversity-oriented decoration and ligation of fullerenes, herein we report the first C_{60} derivatization strategy applying isocyanide-based multicomponent reactions. The approach comprises the use of Passerini and Ugi reactions for assembling pseudo-peptidic scaffolds on carboxylic acid-functionalized fullerenes. Representative compounds were also evaluated as photosensitizers for photodynamic activity showing promising results.

* This chapter was pusblished: Ravanello, B. B.; Seixas, N.; Rodrigues, O. E. D.; da Silva, R. S.; Villetti, M. A.; Frolov, A.; Rivera, D. G.; Westermann, B.; *Chem. Eur. J.* **2018**, 24, 9788-9793.

2.1 Introduction

The development of novel functionalization and derivatization methods for carbon-based materials such as fullerenes, graphene and nanotubes is a crucial step in the pursuit of new properties and applications.[1-3] Functionalized fullerenes have found remarkable utilization in areas as diverse as material science, medicinal chemistry and plant biology, which make the tailor-made decoration of this molecular architecture a fascinating goal in modern synthetic chemistry.[4-8] However, an underexplored strategy with this class of material is the implementation of methods capable to generate large sets of dissimilarly functionalized fullerenes for screening their physico-chemical properties or biological activity. Isocyanide-based multicomponent reactions are among the chemical processes with the greatest diversity and complexity-generation capacity and so, in an endeavour to provide an approach enabling the rapid exploration of the broader exo-fullerene chemical space, we describe the first implementation of IMCRs in fullerene chemistry.

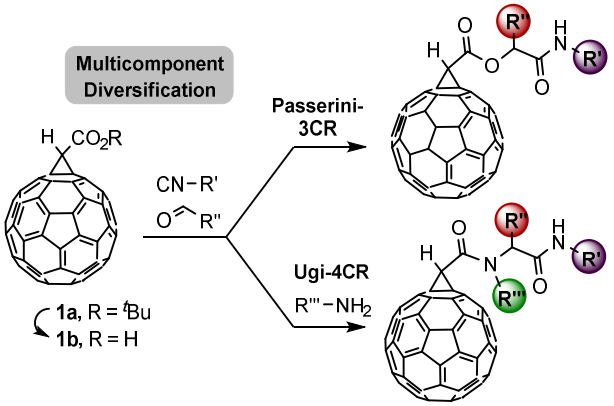
Peptido-fullerenes are of notable interest due to their biological and medicinal relevance, and they have been previously prepared employing standard coupling protocols.[9] Despite the efficacy of this peptide chemistry, such couplings are not diversity-generating *per se* and are fixed to amino and acid components. Instead, the Ugi and Passerini reactions produce unique *N*-substituted and depsi-peptide skeletons, respectively, incorporating up to four elements of diversity, including those arising from the oxo and the isocyanide components.

The use of fullerenes derivatives in photodynamic therapy has been the focus of attention in recent years, where literature reports demonstrate the ability of fullerenes to generate reactive oxygen species such as singlet oxygen, superoxide radicals and hydroxyl radicals. Through the irradiation of light in harmless and specific wavelengths, is possible to use these ROS for the treatment of different kinds of tumours and other diseases, diminishing side effects and improving the safety of this treatment.

2.2 Synthetic Strategy

The concept of using a multicomponent approach for the diversity driven decoration of fullerenes has remained elusive so far. We sought implementing this methodology by using the Ugi four-component and Passerini three-component reactions for the installation of pseudo-peptidic exo-fullerene moieties.

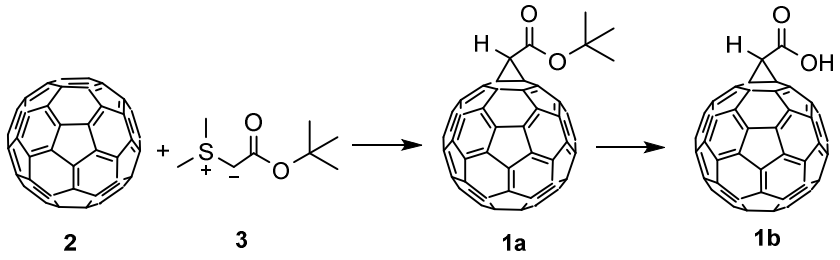
Fullereno-carboxylic acids are among the most widely used substrates in fullerene chemistry, as they are available by a variety of synthetic transformations including the Bingel-Hirsch and Prato reactions.[10,11] As depicted in Scheme 1, this is another advantage of the multicomponent diversification of fullerenes by Ugi and Passerini reactions, as carboxy-functionalized C_{60}, C_{70} and higher ones can be used as carboxylic acid components.



Scheme 1. Multicomponent diversification of fullerene C_{60} by Passerini and Ugi reactions.

2.3 Synthesis of fullerene derivatives

Carboxylated fullerenes, which are readily available *via* the Wilson method (sulfoniumylides) have been selected as starting materials.[12,13] 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. Deprotection leads to the carboxy-modified fullerene **1b** which is suitable to be used in multicomponent reactions (Scheme 2).



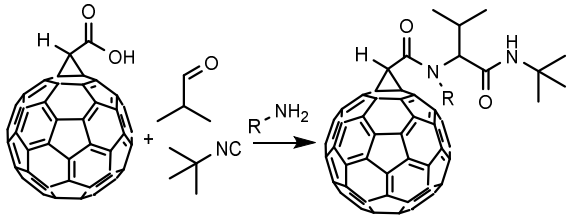
Scheme 2. Synthesis of carboxylated fullerene **1b**.

2.3.1 Synthesis of fullereno-Ugi derivatives

In initial experiments we found out that the Ugi reaction is highly sensitive on the amine component. Aliphatic amines do not provide good substrates for the derivatization of C_{60}, while aromatic amines such as anilines provide excellent reaction yields with a variety of aldehydes and isocyanides. Extensive optimization of the reaction conditions were carried out to assess which factors might be influencing the poor reactivity of aliphatic amines in the Ugi reaction. For this, various solvents and solvent mixtures were tested (chlorobenzene, dichloromethane, methanol, dioxane, trifluoroethanol) but no product formation was detected with aliphatic amines (Me, *i*-Pr, Bn, and *C*-protected amino acids), isobutyraldehyde and *tert*-butyl isocyanide. On the other hand, the use of aniline led to the Ugi products in good yields in all solvent system tested, especially the solvent mixture CH_2Cl_2/CH_3OH 3:1, which provided good substrate solubilization while including a polar protic solvent known to favor Ugi reactions (Table 1). For the reaction time optimization, 48 hours proved the be the best compromise, since additional time had no influence in the yields.

Table 1. Optimization protocol for the Ugi reaction.

Solvent	Yield (%)
C_6H_5Cl	35
CH_2Cl_2	48
CH_3OH	27
CH_2Cl_2 / CH_3OH (3:1)	60
C_6H_5Cl / CH_3OH (2:1)	54
CH_2Cl_2 / CH_3OH (1:1)	55
CH_2Cl_2 / Dioxane (1:1)	50
CF_3CH_2OH	33



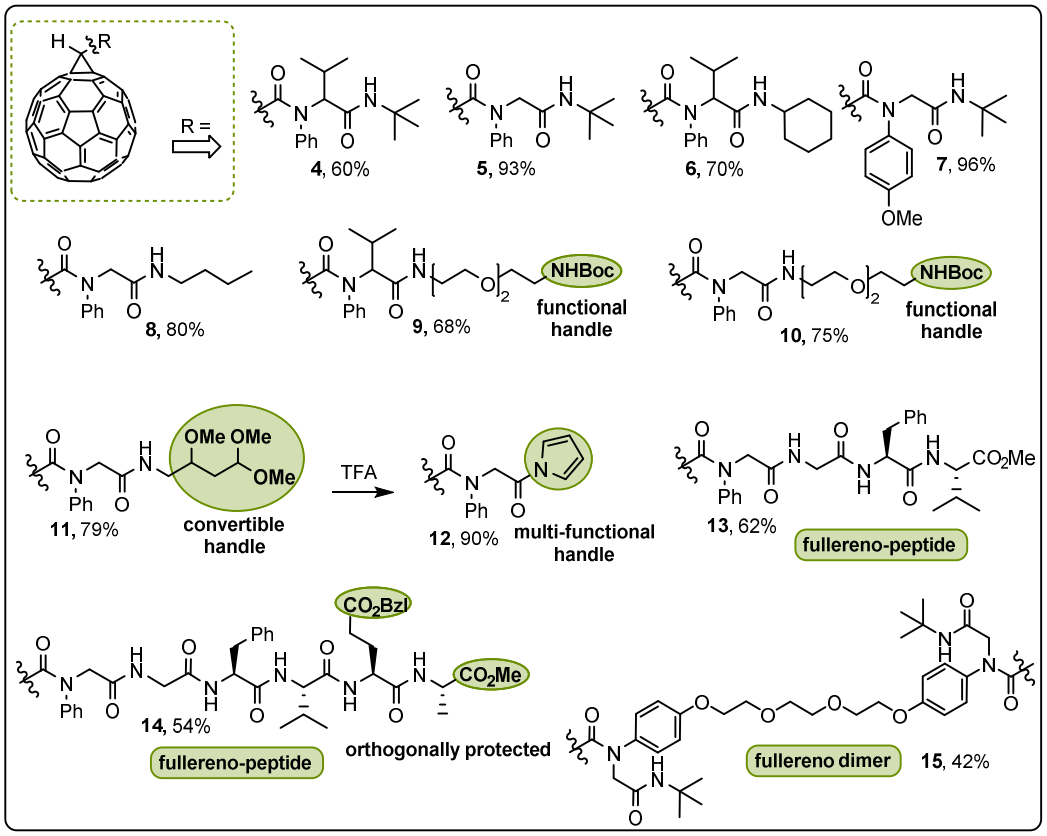
R = Me, *i*-Pr, Bn, and C-protected amino acids ✖
Aniline ✔

Reaction time (h)	Yield (%)
24	39
48	60
72	61

The rationale for superior behavior of aniline might be found in the π-π interactions of this compound with the fullerene structure.[14] This effect can stabilize the aromatic imine (derived from aniline) in a prefered conformation, otherwise not possible with the use of aliphatic amines. Another reasonable explanation is the so-called hydrophobic effect, which may assist the multicomponent reaction by engaging the

hydrophobic imine and C_{60}-cyclopropanecarboxylic acid **1b** with the isocyanide component.[15]

Scheme 3 illustrates the high structural diversity that can be reached in functionalized fullerenes C_{60} by implementing the Ugi reaction with fullerene modified carboxylic acid **1b**. Compounds **4** - **6** were produced in good to excellent yields using commercially available isocyanides, in this case proving that formaldehyde was slightly more effective than isobutyraldehyde as oxo-component. Synthesis of the C_{60}-amino acid-PEG chimeras **9** and **10** highlights how a bifunctional PEG-isocyanide can be used both for improving the solubility (soluble tag) and installing a functional handle for further functionalization. For addressing the scope of the amino component, anilines bearing electron-withdrawing and donating groups were employed, revealing very poor reactivity for the former but excellent results for the latter ones. Thus, 4-methoxyaniline reacted almost quantitatively to render product **7** in 96 % of isolated yield. This result paves the way for the future diversification of the exo-fullerene *N*-aryl peptide skeleton, since more complex *p*-alkyloxy-anilines are readily available building blocks (see chapter 3).

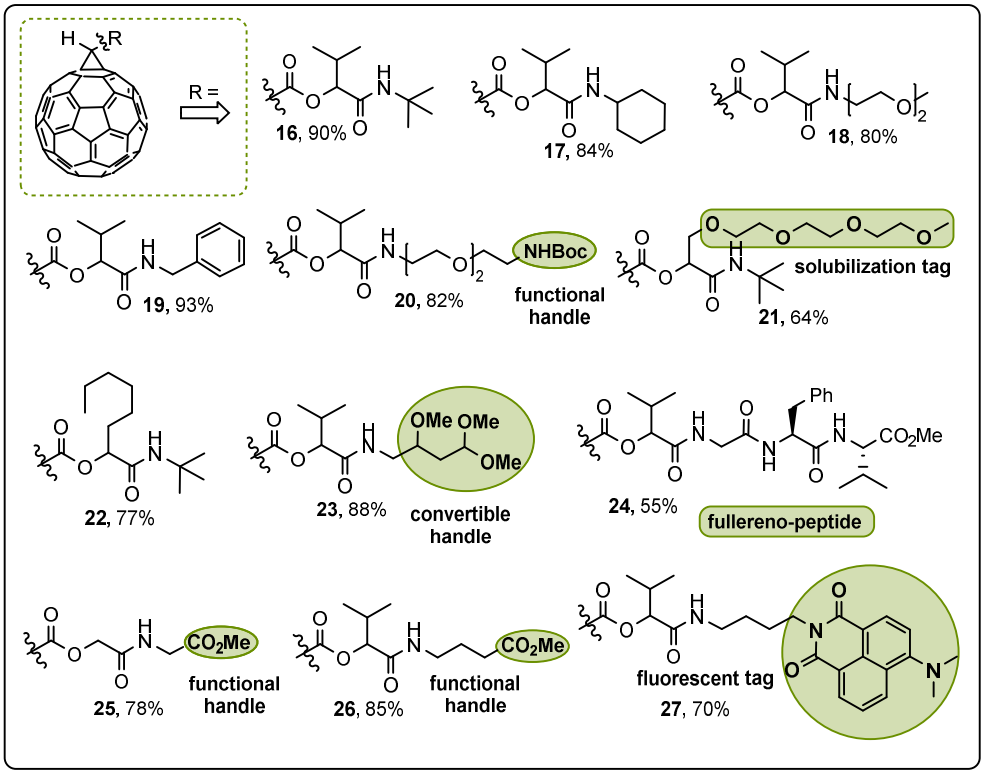


Scheme 3. Chimeric fullerenes C_{60} including *N*-aryl peptoid, PEGs and peptides derived from the Ugi reaction. TFA: Trifluroacetic acid.

The high level of structural complexity arising from the isocyanide component is one of the strongest points of this strategy. This is exemplified with the synthesis of the complex peptido-fullerenes **13** and **14** through the multicomponent ligation of isocyano tetra- and pentapeptides to carboxylic acid **1b** in the presence of aniline and formaldehyde. Indeed, such ligation protocol is also amenable for the incorporation of other biomolecular fragments of biological relevance such as lipids and carbohydrates, as these lipophilic and hydrophilic isocyanides, respectively, are available substrates nowadays. An alternative for the use of structurally complex isocyanides is the use of convertible derivatives, which can be easily transformed into an activated acyl group to enable further derivatization with suitable nucleophile.[16] This concept has never been implemented in fullerene chemistry, and herein it is demonstrated with the multicomponent reaction of carboxylic acid **1b** with the convertible isocyanide 4-isocyanopermethylbutane-1,1,3-triol in the presence of aniline and formaldehyde to furnish Ugi adduct **11** in 79 % yield. This key intermediate functionalized with a convertible handle can be readily transformed into the acyl pyrrole derivative **12** by mild acidic treatment and be further ligated to another molecules bearing e.g., an amino group. Notably is the formation of the fullerene dimer **15**, obtained in a single step with the use of a bis-anilino starting material.

2.3.2 Synthesis of fullereno-Passerini derivatives

After proving the great potential of the Ugi reaction for the diversity-oriented decoration and ligation of carboxy-fullerenes, we turned to assessing the efficiency of the Passerini reaction for the same purpose. Typically, this latter reaction proceeds better in non-polar solvents and avoids the limiting factor of the amino component as observed for the Ugi reaction, usually comprising a wide scope of the oxo-component, including complex ketones. As depicted in Scheme 4, we initially focused on the assessing the substrate scope with varied aldehydes and isocyanides and later on the installation of biologically or chemically relevant moieties. Thus, functionalized fullerenes C_{60} **16**, **17** and **19** were produced in excellent yields using isobutyraldehyde and varying the isocyanide component, while **23**, **25**, and **26** were also obtained with efficiency using formaldehyde and isocyano components bearing a convertible and a functional handle (methyl ester), respectively. We also sought to prove that the aldehyde component could be an additional source of exo-fullerene functional diversity. For this, carboxylic acid **1b** and *tert*-butyl isocyanide were reacted with aldehydes bearing a PEG chain (**21**) and a long aliphatic chain (**22**), which demonstrated the feasibility of using this component as a powerful diversity element.

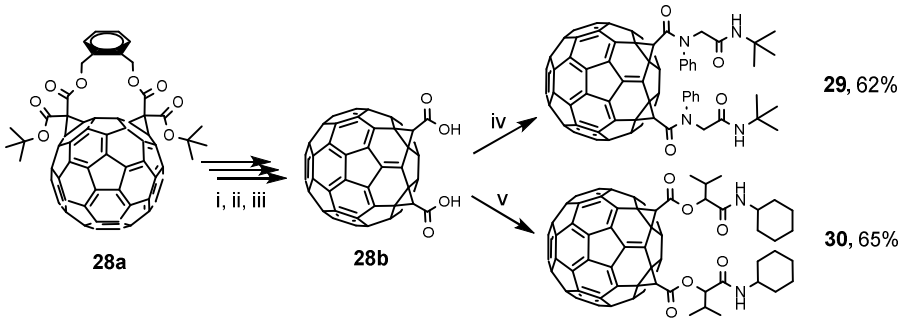


Scheme 4. Chimeric fullerenes C_{60} including depsi-peptides, PEGs and fluorescent labels derived from the Passerini reaction.

The installation of PEG chains can be used to fulfill the double objective of improving the solubility (soluble tag) of C_{60} derivatives and introducing reactive handles for further functionalization. Both purposes can be also accomplished by exploiting the isocyanide component, as proven in the synthesis of compounds **18** and **20** from PEG-isocyanides. Alternatively, the ligation of isocyanopeptides enabled the synthesis of chimeric C_{60}-depsi-peptide **24** in good yield, proving the second case that the simultaneous functionalization of fullerenes with structurally different skeletons (peptide and PEG) is a possible by means of this multicomponent strategy. Finally, synthesis of the fluorescently labeled fullerene **25** further demonstrates the potential of this strategy for the tailor-made exo-decoration of C_{60} with complex and chemically relevant scaffolds.

2.3.3 Bis-functionalized products

An extension of the MCR decoration methods is shown in Scheme 5 with the synthesis of bis-antenary fullerenes C_{60} bearing two pseudo-peptidic moieties. By using bis-malonates with *o*-xylene diol tethers, the fullereno bis-adduct **28a** was obtained with a cis-2 configuration (Nierengarten nomenclature) according to a reported procedure.[17] After a sequence of deprotection, decarboxilation and deprotection the product **28b** was obtained and subjected to double Passerini and Ugi reactions to afford the bis-adducts **29** and **30** in good yields. With these simple examples, we highlighted the possibility of increasing even more the molecular complexity by incorporating into a bifunctional C_{60} up to six components in one step (Scheme 5).



Scheme 5. Bis-adducts of the Ugi and Passerini reaction. i) **28a**, TFA, CH_2Cl_2, r.t., 4 h; ii) 4-dimethylaminopyridine (DMAP), tetrahydrofuran (THF), r.t., 24 h; iii) BBr_3, CH_2Cl_2, r.t., 16 h; v) **28b**, *tert*-butyl isocyanide, formaldehyde, aniline, CH_2Cl_2:MeOH (3:1), r.t., 48 h; iv) **28b**, cyclohexyl isocyanide, isobutyraldehyde, CH_2Cl_2:MeOH (3:1), r.t., 48 h.

2.4 Evaluation of C_{60} derivatives as photosensitizers

Currently, fullerenes and their derivatives have been studied as photosensitizers mediating photodynamic therapy (PDT) in various diseases. The efficiency is related to the generation of cytotoxic singlet oxygen ($^1O_2$), which causes oxidative stress and membrane damage in the treated cells, leading to cell death. The ability of the MCR-decorated fullerenes to produce $^1O_2$ was monitored by the photo-bleaching of 1,3-diphenylisobenzofuran (DPBF) in toluene. For this, compounds **4**, **5**, **6**, **9** and **16** were chosen as representatives of the new fullerene series.

It is well known that DPBF acts as a molecular singlet oxygen scavenger, which is generated by type II photo-processes to produce 1,2-dibenzoylbenzene that does not absorb visible light.[18] Figure 1 depicts the time-dependence decrease in the DPBF

absorbance at 415 nm during irradiation of the fullerene adduct **4** with a 660 nm laser beam. The plot of ln (A_0/A) versus irradiation time gives a straight line (R^2 0.9998) passing through the origin, indicating a first-order kinetic for photo-bleaching of DPBF in the presence of **4** (see insert in Figure 1).

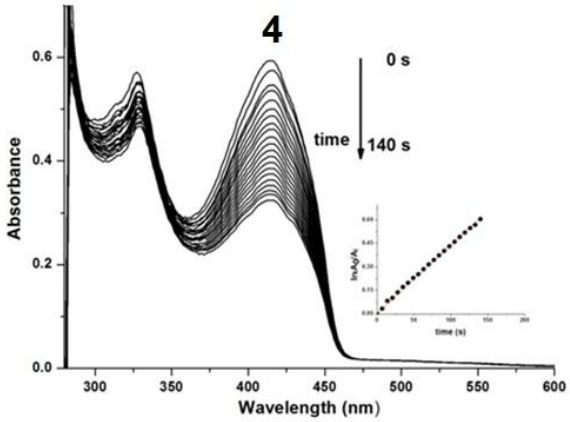


Figure 1. Photooxidation of DPBF in the presence of **4** in toluene. Insert figure shows the first order kinetics.

In this study, the rate constant of photo-oxidation of DPBF sensitized by **4** was k = 4.43x10^{-3} s^{-1}. The high photodynamic activity of this compound may be mainly attributed to the long lifetime of the triplet state to efficiently produce $^1O_2$.[19] Moreover, the kinetic data of DPBF photo-oxidation revealed the ability of **4** to produce $^1O_2$, through determination of singlet oxygen quantum yield (Φ_Δ). The Φ_Δ of **4** was determined by the relative method using fullerene as the reference,[20] in accordance to equation 1:

$$\Phi_\Delta = \Phi_\Delta^{Std} \cdot \frac{k}{k^{Std}} \cdot \frac{I^{Std}}{I} \quad \text{(equation 1)}$$

where Φ_Δ^{std} is the singlet oxygen quantum yield for the standard (1.00 for fullerene in toluene);[21] k and k^{std} are the DPBF photobleaching rate constants in the presence of the respective samples and standard; and I and I^{std} are the rates of light absorption at the irradiation wavelength of laser by the samples and standard, respectively. The measured value of Φ_Δ for **4** was 0.91 indicating that it is very efficient to produce singlet oxygen in this medium.

Encouraged by these results, we analyzed the differences caused by the presence of other substituent in the structure of compounds **5**, **6**, **9** and **16**. Figure 2 depicts the photo-oxidation curves of DPBF sensitized by these fullerene derivatives and the kinetics curves (inserts, Figure 2).

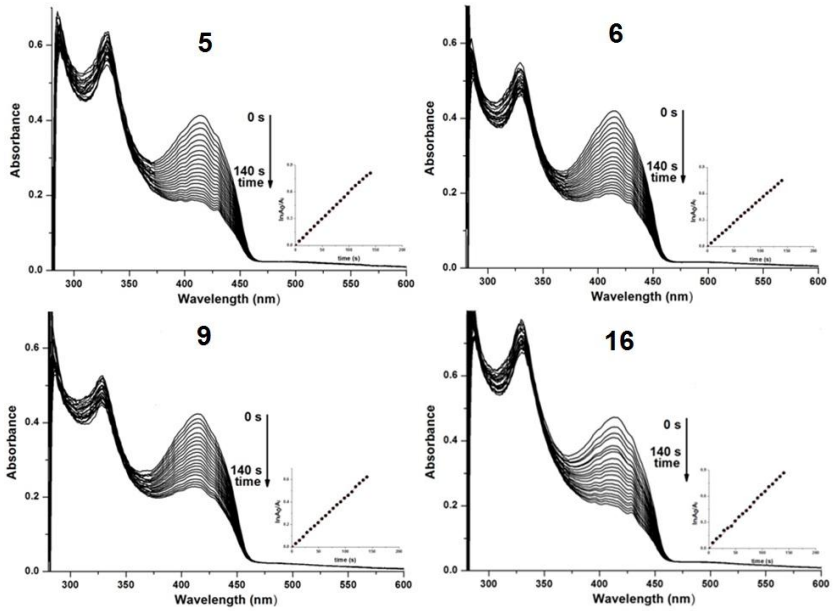


Figure 2. Photooxidation of DPBF in the presence of **5**, **6**, **9** and **16** in toluene; Insert figure shows the first order kinetics profile.

As shown, the DPBF decomposition followed a typical first order kinetics profile. The capacity of production singlet oxygen of these compounds was also evaluated and the Φ_Δ values are depicted in Table 2. As observed, there is a clear relation between the generation of singlet oxygen and the different moieties in the structure of the fullerenes. With the *tert*-butyl group attached to the chimeric fullereno-peptoid **4**, a higher production of cytotoxic $^1O_2$ was observed, as compared with the removal of the isopropyl group in **5**. Furthermore, the cyclohexyl group in **6** also decreased the activity for the $^1O_2$ generation as well as the addition of a polar chain in adduct **9**, that showed a negative effect in this ability (Figure 2). The modification of bisamide **4** to depsipeptide **16** also contributed for decreasing the photoactivity of this type of compound.

Table 2. Singlet oxygen quantum yield (Φ_Δ) of fullerene derivatives in toluene.

Compound	Φ_Δ [20]
C_{60}	1.00
4	0.91
5	0.64
6	0.47
9	0.37
16	0.69

As known, the ability for $^1O_2$ generation of the photosensitizers is related with several factors, including solubility and absence of photosensitizers aggregates in the solution. In this case, variation in the photoactivity for the compounds evaluated could be associated to the higher solubility in toluene for the less polar compounds, as well as the lower aggregation for the most steric hindered fullerenes, containing the *tert*-butyl group.

2.5 Conclusion

In conclusion we have shown successfully that IMCR reactions are very much suitable to diversify fullerenes, taking advantage of the attractive protocol to produce new derivatives. The Passerini and Ugi reactions show a quite high scope of starting materials to be used, however, the Ugi reaction seems to be restricted to aromatic amines. Investigations in the $^1O_2$ formation revealed appealing quantum yields, making them eligible for further evaluation.

2.6 Experimental Part

2.6.1 General information

All commercial reagents were used without further purification. Column chromatography was carried out with Merck silica gel 60 (0.040 - 0.063 mm) and analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 aluminium sheets. Proton and carbon nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were recorded at 25 °C in the respective solvents on an Agilent DD2 400 NMR spectrometer at 399.917 and 100.570 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to TMS (^{1}H NMR) and to residual solvent signal (^{13}C NMR). High resolution mass spectra were obtained from an Orbitrap Elite mass spectrometer (Thermofisher Scientific, Bremen, Germany) equipped with an ESI electrospray ion source (spray voltage 4.0 kV; capillary temperature 275 °C, source heater temperature 40 °C; FTMS resolution 60.000). Electrospray ionization mass spectra (ESI-MS) were recorded on a API 3200 system, Triple Quadrupole MS (AB Sciex) equipped with ESI electrospray ion source (positive spray voltage 5.5 kV, negative spray voltage 4.5 kV, and source heater temperature 400 °C). MALDI-TOF mass spectra were acquired on a Bruker Ultraflex III-MALDI-TOF/TOF mass spectrometer (Bruker Daltonics, Bremen, Germany). The samples solubilized in toluene (0.5 µL) were mixed with the equal

volume of a 0.1 % w/v *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene] malononitrile on acetone (DCTB, matrix) on a stainless steel target and dried under air. The analysis was performed in a reflector positive ion mode, using the source and reflector voltages of 25 and 26.3 kV, respectively. Desorption/ionization of the analytes was achieved by a YAG 354 nm laser.

2.6.2 Synthesis

2.6.2.1 Synthesis of starting materials

Methyl 4-isocyanobutanoate (S1): A solution of methyl 4-aminobutanoate-hydrochloride (3.0 g, 19 mmol) in ethyl formate (25 mL) was refluxed for 20 h, followed by the evaporation of all volatiles to yield the corresponding product methyl 4-formylaminobutanoate as colourless oil. A solution of the formamide (2.5 g, 17 mmol) in dichloromethane (40 mL) was added in a round-bottom flask under nitrogen atmosphere. Diisopropylamine (7.0 mL, 50 mmol) was added and the reaction mixture was cooled to 0 °C. After the dropwise addition of phosphorus oxychloride (1.9 mL, 20 mmol) the reaction mixture was warmed to room temperature and allowed to stir for 2 h. The reaction was quenched with Na_2CO_3 (3.4 g in 15 mL dest. H_2O). The resulting suspension was stirred further 30 min, diluted with water and the organic layer was separated. The aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the organic solvent removed under reduced pressure. The product was purified by column chromatography (*n*-hexane/ethyl acetate: 3/1) to afford **S1**. Light yellow oil; Yield 60 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.71 (s, 3H), 3.50 (ddt, *J* = 8.6, 3.9, 2.0 Hz, 2H), 2.52 (t, *J* = 7.1 Hz, 2H), 2.00 (dqt, *J* = 11.9, 4.9, 2.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.49, 156.72, 51.79, 40.72, 30.10, 24.21.

4-*N*,*N*-Dimethylamino-1,8-naphthalic anhydride (S2): The synthesis of **S2** was performed according to previous reports in the literature.[22] 4-Bromo-1,8-naphtalic anhydride (7.0 g, 25.2 mmol) and *n*-butanol (170 mL) were added to a round-bottom flask equipped with a reflux condenser. The solution was brought to reflux and 11 mL of 3-*N,N*-dimethylaminopropionitrile was added slowly. The reaction mixture was stirred at reflux overnight and cooled with an ice bath until the formation of a yellow precipitate. The solid was filtered and washed with *n*-hexane to give the desired product. Yellow solid; Yield: 89 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.58 (dd, *J* = 7.3, 1.2

Hz, 1H), 8.51 - 8.45 (m, 2H), 7.69 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 3.18 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.68, 160.44, 134.92, 133.13, 132.89, 132.72, 124.99, 124.90, 119.28, 113.22, 44.58.

***tert*-Butyl (4-(6-(dimethylamino)-1,3-dioxo-1*H*-benzo[d,e]isoquinolin-2(3*H*)yl)butyl carbamate (S3):** The synthesis of **S3** was performed according to previous reports in the literature.[22] **S2** (6.1 g, 25.1 mmol) and absolute ethanol (400 mL) were added to a round-bottom flask equipped with a reflux condenser. *N*-(*tert*-butoxycarbonyl)-1,4-diaminobutane was added to the mixture and the solution was brought to reflux. After 30 min. the solvent was removed under reduced pressure and the product purified by flash chromatography (ethyl acetate), yielding **S3**. Orange solid; Yield: 54 %; R_f 0.25 (*n*-hexane/ethyl acetate: 6/4); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56 (d, *J* = 7.2, 1.2 Hz, 1H), 8.48 - 8.41 (m, 2H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 4.22 - 4.15 (m, 2H), 3.24 - 3.17 (m, 2H), 3.11 (s, 6H), 1.81 - 1.71 (m, 2H), 1.66 - 1.59 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.55, 164.01, 156.92, 155.88, 132.60, 131.14, 130.98, 130.19, 125.25, 124.84, 123.00, 114.92, 113.27, 78.93, 44.74, 40.22, 39.61, 28.38, 27.51, 25.46.

2-(4-Aminobutyl)-6-(dimethylamino)-1*H*-benzo[d,e]isoquinoline-1,3(2*H*)-dione (S4): The synthesis of **S4** was performed according to previous reports in the literature.[22] **S3** (1.1 g, 2.5 mmol) and CH_2Cl_2/TFA (40 mL, 1:1) were added to a round-bottom flask. The reaction mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure to yield the corresponding product, Yellow solid; Yield: 95 %; R_f 0.43 (ethyl acetate/methanol: 8/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.32 - 8.26 (m, 2H), 7.52 (dd, *J* = 8.5, 7.3 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 4.10 (t, *J* = 6.6 Hz, 2H), 3.13 (s, 2H), 3.05 (s, 6H), 1.89 - 1.75 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.67, 164.19, 157.06, 132.82, 131.39, 131.07, 130.05, 124.81, 124.65, 122.39, 113.97, 113.09, 44.64, 39.63, 38.98, 24.81, 24.72.

6-(Dimethylamino)-2-(4-isocyanobutyl)-1*H*-benzo[d,e]isoquinoline-1,3(2*H*)-dione (S5): Compound **S5** was prepared by the same method as methyl 4-isocyanobutanoate (**S1**) starting from **S4** (2.0 g, 6.4 mmol). Orange solid; Yield: 54 %; R_f 0.42 (*n*-hexane/ethyl acetate: 6/4); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.57 (d, *J* = 7.3, 1.2 Hz, 1H), 8.50 - 8.42 (m, 2H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 4.22

(t, *J* = 6.9 Hz, 2H), 3.48 (t, *J* = 6.6, 1.9 Hz, 2H), 3.12 (s, 6H), 1.94 - 1.76 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.63, 164.06, 157.07, 156.02, 132.76, 131.32, 131.11, 130.26, 125.23, 124.86, 122.86, 114.67, 113.28, 44.75, 41.23, 38.80, 26.66, 25.10.

***tert*-Butyl (2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamate (S6):** 2,2′-(Ethylenedioxy) bis-ethylamine (1.0 g, 6.74 mmol) was dissolved in a mixture of dioxane (10 mL), H_2O (10 mL) and NaOH (1 N, 15 mL). The mixture was cooled to 0 °C and a solution of di-*tert*-butyl dicarbonate (320 mg, 1.5 mmol) in dioxane (5 mL) was added dropwise. The ice bath was removed and the reaction mixture was stirred at room temperature for 18 h. Dioxane was evaporated and the residue extracted with ethyl acetate (3 x 25 mL). The solvent was removed and the product was used in the next step without further purification. Light brown oil; Yield: 85 %.

***tert*-Butyl (2-(2-(2-isocyanoethoxy)ethoxy)ethyl)carbamate (S7):** Isocyanide **S7** was prepared by the same method as **S1** starting from **S6** (1.5 g, 6.0 mmol). Brown oil; Yield: 77 %; ^{1}H NMR (400 MHz, $CDCl_3$) = δ 3.76 - 3.53 (m, 10H), 3.34 - 3.30 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) = δ 157.45, 155.89, 79.21, 70.77, 70.29, 70.13, 68.62, 41.69, 40.29, 28.37.

1-Isocyano-2-(2-methoxyethoxy)ethane (S8): Isocyanide **S8** was prepared by the same method as **S1** starting from 2-(2-methoxyethoxy) ethaneamine (1.0 g, 8.4 mmol). The dried product was used in the next step without further purification. Yellow oil; Yield: 70 %.

Methyl (2-isocyanoacetyl)-L-phenylalanyl-L-valinate (S9): The synthesis of (2-isocyanoacetyl)-L-phenylalanyl-L-valinate (**S9**) was performed according to previous literature reports.[23] Potassium isocyanoacetate (50 mg, 0.43 mmol) and methyl L-phenylalanyl-L-valinate (90 mg, 0.33 mmol) were solubilized in THF (5 mL), followed by the addition of triethylamine (0.1 mL, 0.37 mmol). The mixture was cooled to -10 °C, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU, 160 mg, 0.5 mmol) was added and the reaction mixture was vigorously stirred for 12 h at room temperature. 2/3 of the solvent volume was evaporated and ethyl acetate (20 mL) was added. The mixture was washed with 1 N $NaHCO_3$ aqueous solution (20 mL), 1 N HCl aqueous solution (20 mL) and 1 N $NaHCO_3$ aqueous solution (20 mL), respectively,

and extracted with ethyl acetate (3x 25 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure, keeping the temperature below 35 °C. The dried product was used in the next step without further purification. Yellow oil; Yield: 40 %.

Methyl (2S,5S,8S,11S)-11-benzyl-5-(3-(benzyloxy)-3-oxopropyl)-14-isocyano-8-isopropyl-2-methyl-4,7,10,13-tetraoxo-3,6,9,12-tetraazatetradecanoate (S10): Compound **S10** was prepared by the same method as **S9** starting from Phe-Val-Asp(OBz)-AlaOMe (39 mg, 0.05 mmol). The dried product was used in the next step without further purification. Yellow oil; Yield: 33 %.

***tert*-Butoxycarbonyl)methylsulfonium bromide (S11):** The synthesis of the sulfonium salt **S11** was performed according to previous literature reports.[13] Dimethyl sulfide (1.5 mL, 20 mmol), *tert*-butyl bromoacetate (3 mL, 20 mmol) and acetone (20 mL) were stirred in a two neck round bottom flask under nitrogen atmosphere for 18 h. After the reaction time the solid formed was filtered, washed with acetone and dried under vacuum to obtain **S11**. The dried product was used in the next step without further purification. Light yellow solid; Yield 72 %.

***tert*-Butyl (dimethylsulfanylidene)acetate (S12):** The synthesis of **S12** was performed according to previous literature reports.[13] To a solution of **S11** (3.85 g, 15 mmol) in dichloromethane (20 mL), cooled at 0 °C, was added a saturated aqueous solution of K_2CO_3 (10 mL), keeping the temperature below 10 °C. After stirring for 1.5 h, a 50 % aqueous solution of NaOH (2 mL) was added portionwise, keeping the temperature below 5 °C. The mixture was stirred for 3 h and filtered. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to give compound **S12**. The dried product was used in the next step without further purification. Yellow solid; Yield: 90 %.

1,2-Bis{[(*tert*-butoxycarbonyl)acetoxy]methyl}benzene (S13): Mono-*tert*-butyl-malonate (1.0 g, 6.25 mmol) was dissolved in acetonitrile (20 mL) and heated to reflux. To this solution was added dibromo-*o*-xylene (790 mg, 3.0 mmol) and triethylamine (0.9 mL, 6.25 mmol), respectively. The reaction mixture was stirred for 8 h under reflux

and the solvent was removed under reduced pressure. The mixture was diluted in dichloromethane and washed with a saturated aqueous solution of NH_4Cl, NaCl and H_2O. After evaporation of the organic layer under reduced pressure, the crude product was purified by column chromatography (gradient *n*-hexane to ethyl acetate) to give product **S13**. Colourless oil; Yield: 71 %.

61,62-Di(*tert*-butyl)-*endo*,*endo*-61,62-(*o*-phenylenedimethylene)-1,2:7,21-bis(methano)[60] fullerene-61,61,62,62-tetracarboxylate (28a): Bis-functionalized product **28a** was synthesized according to previous literature reports.[17] A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.23 mL, 1.5 mmol) in chlorobenzene (5 mL) was added to a solution of fullerene C_{60} (360 mg, 0.5 mmol), iodine (380 mg, 1.5 mmol) and **S13** (230 mg, 0.55 mmol) in chlorobenzene (100 mL), at room temperature, under nitrogen atmosphere. The reaction mixture was stirred for 4 h, the solvent was removed under reduced pressure and the crude material was purified by column chromatography (*n*-hexane/CH_2Cl_2: 7/3) to give **28a**. Dark red solid; Yield: 35 %; R_f 0.54 (CH_2Cl_2/*n*-hexane: 6/4); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (s, 1H), 7.41 (t, *J* = 6.9 Hz, 1H), 7.29 (d, *J* = 6.9 Hz, 1H), 5.88 (d, *J* = 12.9 Hz, 2H), 5.19 (d, *J* = 12.9 Hz, 2H), 1.55 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) 163.30, 161.63, 148.83, 147.43, 147.38, 147.21, 146.15, 145.97, 145.71, 145.64, 145.53, 145.26, 145.09, 145.02, 144.46, 144.43, 144.15, 144.07, 143.85, 143.62, 143.48, 143.21, 143.07, 142.24, 141.17, 140.92, 139.77, 137.15, 136.58, 136.18, 135.75, 135.22, 128.53, 126.17, 123.14, 84.82, 70.85, 67.21, 67.12, 50.11, 27.74.

61,62-Dihydrogen-*endo*,*endo*-61,62-(*o*-phenylenedimethylene)-1,2:7,21-bis(methano)[60] fullerene-61,61,62,62-tetracarboxylate (S14): Bis-carboxylate **S14** was synthesized according to previous literature reports.[17] TFA (10 mL) was added *via* syringe under nitrogen at room temperature to a solution of **28a** (72 mg) in dry dichloromethane (40 mL). After stirring for 4 h the precipitate formed was filtered, washed with dichloromethane and dried under high vacuum to give product **S14**. The dried product was used in the next step without further purification. Dark red solid; Yield: 69 %.

***endo*,*endo*-(*o*-Phenylenedimethylene)-1,2:7,21-bis(methano)-[60]fullerene-61,62 dicarboxylate (S15):** Bis-functionlized **S15** was synthesized according to previous literature reports.[17] DMAP (4 mg), dissolved in dry THF (3 mL), under nitrogen

atmosphere at room temperature, was added *via* syringe to a solution of **S14** (50 mg) in dry THF (50 mL) and the mixture was stirred for 20 h. The crude product was concentrated under reduced pressure and after column chromatography using dichloromethane as eluent, product **S15** was obtained. Brown solid; Yield: 65 %.

***endo*,*endo*-1,2:7,21-Bis(methano)[60] fullerene-61,62-dicarboxylic acid (28b):** Dicarboxylic acid **28b** was synthesized according to previous literature reports.[17] BBr_3 (96 mg) was added dropwise *via* syringe under nitrogen atmosphere at -10 °C to a vigorously stirred solution of **S15** (31 mg) in dry dichloromethane (40 mL). The mixture was stirred for 15 h at room temperature, followed by the addition of water to quench the excess reactant. The solid formed was collected by filtration and dried under high vacuum to give **28b**. Brown solid; Yield: 83 %.

***tert*-Butyl [60]fullerenoacetate (1a):** To a toluene solution (100 mL) of fullerene C_{60} (144 mg, 0.2 mmol), was added dropwise a toluene solution (5 mL) of **S12** (33 mg, 0.19 mmol) at room temperature, under nitrogen atmosphere. After stirring for 18 h the reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography to afford product **1a**. Brown solid; Yield: 55 %. MALDI-TOF: *m/z* calculated for $[C_{66}H_{10}O_2]^+$: 834.068, found: 834.257.

[60]Fullerenoacetic acid (1b): A toluene solution (50 mL) of *tert*-butyl [60]fullereno acetate **1a** (84 mg, 0.11 mmol) and *p*-TsOH.H_2O (42 mg, 0.25 mmol) was refluxed for 8 h to afford a suspension. The precipitate was filtrated and washed with toluene (50 mL) and water (20 mL). The remaining solid was dissolved in a 1:1 mixture of dichloromethane and dioxane (30 mL) and filtered again. The filtrate was concentrated under reduced pressure to afford product **1b**. Dark brown solid; Yield: 80 %; MALDI-TOF: *m/z* calculated for $[C_{62}H_2O_2]^+$: 778.055, found: 778.128.

2.6.2.2 Synthesis of Ugi products

General procedure for the Ugi reaction: Aldehydes (0.015 mmol, 1.2 equiv.) and corresponding amines (0.015 mmol, 1.2 equiv.) were added to a round bottom flask containing 5 mL of methanol and stirred for 2 hours at room temperature. The recently formed imine was added to a suspension of fullerenoacetic acid **1b** (0.0125 mmol, 1.0

equiv.) in dichloromethane (15 mL) followed by the addition of the corresponding isocyanide (0.015 mmol, 1.2 equiv.). The reaction mixture was stirred for 48 hours, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel to afford the corresponding Ugi products.

Ugi product 4: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1.4 µL, 0.015 mmol), aniline (1.4 µL, 0.015 mmol) and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (*n*-hexane/CH_2Cl_2: 1/2) yielded **4** (7.6 mg, 60 %) as a brown solid; R_f 0.57 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 6.73 (s, 1H), 4.56 (s, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 2.52 - 2.40 (m, 1H), 1.40 (s, 9H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.99, 165.40, 147.97, 147.29, 147.19, 145.54, 145.19, 145.16, 145.10, 145.06, 144.67, 144.63, 144.57, 144.49, 144.39, 144.38, 144.36, 144.34, 143.86, 143.61, 143.18, 143.16, 143.13, 142.98, 142.92, 142.87, 142.81, 142.32, 142.30, 142.17, 142.13, 142.03, 141.11, 141.08, 140.92, 140.89, 139.80, 138.98, 138.90, 136.22, 136.17, 129.98, 129.39, 129.24, 72.78, 72.62, 70.57, 51.35, 43.44, 28.65, 26.97, 20.33, 19.63; MALDI-TOF: *m/z* calculated for $[C_{77}H_{24}N_2O_2]^+$: 1008.184, found:1008.083.

Ugi product 5: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.6 mg, 0.015 mmol), aniline (1.4 µL, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (*n*-hexane/CH_2Cl_2: 1/3) yielded **5** (11.2 mg, 93 %) as a brown solid; R_f 0.20 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 7.9 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 6.21 (s, 1H), 4.61 (s, 1H), 4.46 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.20, 164.87, 147.89, 146.95, 145.53, 145.20, 145.17, 145.08, 144.68, 144.64, 144.59, 144.49, 144.43, 144.35, 143.87, 143.62, 143.20, 143.12, 142.98, 142.92, 142.88, 142.81, 142.31, 142.20, 142.18, 142.03, 141.71, 141.11, 140.93, 139.22, 136.31, 130.46, 129.36, 128.00, 72.44, 55.46, 51.62, 41.96, 28.74; MALDI-TOF: *m/z* calculated for $[C_{74}H_{18}N_2O_2]^+$: 966.137, found: 966.041.

Ugi product 6: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1.4 µL, 0.015 mmol), aniline (1.4 µL, 0.015 mmol), and cyclohexyl isocyanide (1.9 µL, 0.015 mmol). Isolation by column chromatography (*n*-hexane/CH_2Cl_2: 1/2) yielded **6** (9.0 mg, 70 %) as a brown solid; R_f 0.33 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 4.54 (s, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 3.88 - 3.77 (m, 1H), 2.64 - 2.50 (m, 1H), 2.01 - 1.92 (m, 2H), 1.76 - 1.67 (m, 2H), 1.64 - 1.58 (m, 1H), 1.45 - 1.28 (m, 5H), 1.26 - 1.21 (m, 3H), 1.05 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.96, 165.59, 148.01, 147.91, 147.20, 147.02, 145.55, 145.53, 145.20, 145.16, 145.14, 145.06, 145.04, 144.66, 144.63, 144.59, 144.57, 144.48, 144.39, 144.34, 144.31, 143.87, 143.61, 143.60, 143.20, 143.18, 143.15, 142.98, 142.91, 142.86, 142.80, 142.31, 142.29, 142.16, 142.15, 142.04, 142.02, 141.12, 141.07, 140.92, 140.86, 139.15, 139.00, 136.21, 136.16, 130.09, 129.40, 129.06, 72.74, 72.51, 60.37, 48.24, 43.34, 32.96, 32.87, 26.93, 25.58, 24.78, 24.75, 20.43, 19.70; MALDI-TOF: *m/z* calculated for $[C_{79}H_{26}N_2O_2]^+$: 1034.199, found: 1034.101.

Ugi product 7: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.6 mg, 0.015 mmol), 4-methoxyaniline (1.9 mg, 0.015 mmol) and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **7** (11.9 mg, 96 %) as a brown solid; R_f 0.15 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 - 7.64 (m, 2H), 7.10 - 7.04 (m, 2H), 6.19 (s, 1H), 4.62 (s, 1H), 4.42 (s, 2H), 3.85 (s, 3H), 1.39 (s, 9H);^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.33, 165.21, 159.92, 147.99, 147.00, 145.53, 145.20, 145.16, 145.09, 145.07, 144.68, 144.64, 144.58, 144.43, 144.34, 143.88, 143.62, 143.20, 143.12, 142.98, 142.92, 142.89, 142.81, 142.33, 142.20, 142.18, 142.03, 141.12, 140.93, 139.32, 136.35, 134.36, 129.15, 115.54, 72.51, 55.67, 51.57, 41.83, 28.73; MALDI-TOF: *m/z* calculated for $[C_{75}H_{20}N_2O_3]^+$: 996.147, found: 996.045.

Ugi product 8: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.6 mg, 0.015 mmol), aniline (1.4 µL, 0.015 mmol) and *n*-butyl isocyanide (1.6 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **8** (9.7 mg, 80 %) as a brown solid; R_f 0.15 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 6.36 (s, 1H), 4.63 (s, 1H), 4.55 (s, 2H), 3.35 (q,

J = 7.3, 2H), 1.55 - 1.50 (m, 2H), 1.45 - 1.31 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.93, 165.12, 147.87, 146.93, 145.53, 145.22, 145.18, 145.08, 145.06, 144.69, 144.64, 144.60, 144.44, 144.35, 143.88, 143.62, 143.20, 142.99, 142.93, 142.89, 142.81, 142.31, 142.23, 142.18, 142.03, 141.74, 141.12, 140.93, 139.18, 136.31, 130.47, 129.38, 127.90, 72.39, 54.66, 41.87, 39.55, 31.63, 20.17, 13.84; MALDI-TOF: *m/z* calculated for $[C_{74}H_{18}N_2O_2]^+$: 966.137, found: 966.982.

Ugi product 9: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1.4 µL, 0.015 mmol), aniline (1.4 µL, 0.015 mmol) and *tert*-butyl (2-(2-(2-isocyanoethoxy) ethoxy)ethyl)carbamate **S7** (3.9 mg, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 9/1) yielded **9** (10.1 mg, 68 %) as a brown solid; R_f 0.55 (CH_2Cl_2/ethyl acetate: 7/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.16 (s, 1H), 5.17 - 5.09 (m, 1H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.55 (s, 1H), 3.67 - 3.60 (m, 6H), 3.58 - 3.52 (m, 4H), 3.35 - 3.30 (m, 2H), 2.53 - 2.38 (m, 1H), 1.45 (s, 9H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.03, 165.47, 156.00, 147.90, 147.17, 145.52, 145.19, 145.16, 145.13, 145.06, 144.66, 144.63, 144.59, 144.56, 144.49, 144.38, 144.30, 144.26, 143.84, 143.61, 143.59, 143.17, 143.14, 143.12, 142.98, 142.91, 142.87, 142.80, 142.32, 142.29, 142.21, 142.16, 142.04, 142.02, 141.13, 141.07, 140.89, 140.81, 139.72, 138.96, 138.77, 136.21, 136.16, 129.94, 129.34, 129.21, 72.85, 72.60, 70.35, 70.29, 69.67, 43.46, 40.43, 39.29, 28.47, 26.98, 20.29, 19.76; MALDI-TOF: *m/z* calculated for $[C_{77}H_{24}N_2O_2]^+$: 1183.268, found: 1183.127.

Ugi product 10: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.6 mg, 0.015 mmol), aniline (1.4 µL, 0.015 mmol) and *tert*-butyl (2-(2-(2-isocyanoethoxy)ethoxy) ethyl)carbamate **S7** (3.9 mg, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 9/1) yielded **10** (10.7 mg, 75 %) as a brown solid; R_f 0.45 (CH_2Cl_2/ethyl acetate: 7/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.7 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 6.66 (s, 1H), 5.07 (s, 1H), 4.64 (s, 1H), 4.58 (s, 2H), 3.68 - 3.60 (m, 6H), 3.60 - 3.52 (m, 4H), 3.38 - 3.27 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.89, 164.87, 156.01, 148.01, 147.02, 145.58, 145.18, 145.14, 145.11, 145.05, 145.03, 144.72, 144.67, 144.60, 144.56, 144.50, 144.41, 144.27, 143.88, 143.60, 143.21, 143.09, 142.96, 142.89, 142.85, 142.76,

142.31, 142.26, 142.19, 142.02, 141.08, 140.85, 139.35, 136.27, 130.34, 129.22, 128.11, 79.32, 72.47, 72.46, 70.33, 70.19, 69.61, 54.05, 41.90, 40.40, 39.51, 28.45. MALDI-TOF: *m/z* calculated for $[C_{81}H_{31}N_3O_6]^+$: 1142.229, found: 1142.586.

Ugi product 11: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.6 mg, 0.015 mmol), aniline (1.4 µL, 0.015 mmol) and 4-isocyano-1,1,3-trimethoxybutane (2.6 mg, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 9/1) yielded **11** (10.5 mg, 79 %) as a brown solid; R_f 0.52 (CH_2Cl_2/ethyl acetate: 7/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.8 Hz, 2H), 7.48 (t, *J* = 7.7 Hz, 1H), 6.51 - 6.47 (m, 1H), 4.61 (s, 1H), 4.58 (s, 2H), 4.53 (t, *J* = 5.8 Hz, 1H), 3.60 - 3.42 (m, 3H), 3.38 (s, 3H), 3.35 - 3.31 (m, 6H), 1.91 - 1.83 (m, 1H), 1.80 - 1.71 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.94, 165.01, 147.98, 147.93, 146.94, 146.82, 145.55, 145.19, 145.14, 145.08, 145.06, 145.03, 144.71, 144.67, 144.60, 144.57, 144.48, 144.42, 144.28, 143.88, 143.86, 143.60, 143.21, 143.08, 142.96, 142.89, 142.85, 142.75, 142.28, 142.18, 142.01, 141.76, 141.08, 140.87, 139.45, 139.40, 136.27, 130.42, 129.28, 127.98, 101.80, 76.07, 72.38, 72.34, 57.07, 54.22, 53.15, 53.11, 41.75, 41.65, 35.04; MALDI-TOF: *m/z* calculated for $[C_{77}H_{24}N_2O_5]^+$: 1056.168, found: 1056.070.

Ugi product 12: Compound **12** was obtained according to previous literature report.[16] The amide **11** (0.055 mmol) was dissolved in 5 % (v/v) TFA in dichloromethane (10 mL) and the mixture was stirred for 1 hour at room temperature before the solvent was evaporated under reduced pressure. Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 9/1) yielded **12** (47.5 mg, 90 %) as a brown solid; R_f 0.52 (CH_2Cl_2/ethyl acetate: 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 - 7.84 (m, 2H), 7.66 - 7.56 (m, 2H), 7.54 -7.48 (m, 1H), 7.40- 7.33 (m, 1H), 6.35 (t, *J* = 2.4 Hz, 2H), 5.24 (s, 2H), 4.68 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.92, 148.01, 146.88, 145.57, 145.19, 145.18, 145.14, 145.06, 145.04, 145.02, 144.79, 144.68, 144.57, 144.49, 144.46, 144.44, 144.29, 144.25, 143.89, 143.61, 143.24, 143.07, 142.95, 142.88, 142.85, 142.73, 142.32, 142.28, 142.21, 142.02, 141.36, 141.07, 140.88, 140.84, 139.57, 136.29, 130.48, 129.54, 128.39, 118.81, 113.92, 72.25, 52.53, 41.42, 29.70; MALDI-TOF: *m/z* calculated for $[C_{74}H_{12}N_2O_2]^+$: 960.922, found: 961.014.

Ugi product 13: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.6 mg, 0.015 mmol), aniline (1.4 µL, 0.015 mmol) and methyl (2-isocyanoacetyl)-L-phenylalanyl-L-valinate **S9** (5.2 mg, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/methanol: 9/1) yielded **13** (9.7 mg, 62 %) as a brown solid; R_f 0.52 (CH_2Cl_2/methanol: 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.35 - 7.28 (m, 2H), 7.25 - 7.20 (m, 3H), 6.99 - 6.91 (m, 2H), 6.32 (d, *J* = 8.5 Hz, 1H), 4.65 (s, 1H), 4.57 - 4.53 (m, 1H), 4.44 (dd, *J* = 8.5, 5.1 Hz, 1H), 4.04 (qd, *J* = 16.8, 5.6 Hz, 1H), 3.69 (s, 1H), 3.20 - 3.06 (m, 2H), 2.19 - 2.06 (m, 1H), 0.95 - 0.79 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.47, 170.43, 167.26, 161.39, 154.36, 153.77, 153.34, 147.03, 146.69, 146.68, 146.64, 146.62, 146.58, 146.57, 146.17, 146.15, 146.13, 146.06, 145.81, 145.36, 145.1 144.48, 144.42, 144.34, 144.31, 143.68, 143.63, 143.53, 142.78, 142.09, 141.52, 137.79, 124.72, 122.54, 120.89, 120.31, 117.90, 117.45, 116.54, 116.45, 116.31, 116.29, 116.05 74.37, 68.00, 57.21, 57.16, 57.13, 57.00, 52.16, 44.80, 32.58, 30.16, 30.14, 30.11, 28.29, 21.78, 21.24, 21.06, 19.73; MALDI-TOF: *m/z* calculated for $[C_{87}H_{32}N_4O_6]^+$: 1229.232, found: 1229.356.

Ugi product 14: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.6 mg, 0.015 mmol), aniline (1.4 µL, 0.015 mmol) and isocyano penta peptide **S10** (10.3 mg, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/methanol: 9/1) yielded **14** (10.6 mg, 54 %) as a brown solid; R_f 0.15 (CH_2Cl_2/methanol: 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.35 - 7.28 (m, 2H), 7.25 - 7.20 (m, 3H), 6.99 - 6.91 (m, 2H), 6.32 (d, *J* = 8.5 Hz, 1H), 4.65 (s, 1H), 4.57 - 4.53 (m, 1H), 4.44 (dd, *J* = 8.5, 5.1 Hz, 1H), 4.04 (qd, *J* = 16.8, 5.6 Hz, 1H), 3.69 (s, 1H), 3.20 - 3.06 (m, 2H), 2.19 - 2.06 (m, 1H), 0.95 - 0.79 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.31, 172.94, 171.71, 170.65, 168.52, 167.74, 165.35, 147.96, 147.87, 147.46, 147.00, 146.83, 145.51, 145.19, 145.13, 145.12, 145.06, 145.04, 144.65, 144.61, 144.57, 144.48, 144.42, 144.39, 144.30, 144.28, 143.84, 143.82, 143.61, 143.59, 143.42, 143.19, 143.17, 143.05, 142.95, 142.89, 142.86, 142.77, 142.75, 142.28, 142.20, 142.17, 142.15, 142.02, 142.00, 141.92, 141.89, 141.07, 140.88, 139.20, 139.19, 136.53, 136.28, 130.43, 129.35, 129.29, 129.15, 128.64, 128.56, 128.30, 128.24, 128.02, 126.98, 72.39, 72.33, 66.68, 59.51, 57.48, 52.13, 48.20, 38.13, 31.91, 31.42, 31.22, 31.18, 30.18, 29.68, 29.34, 22.67, 18.93, 17.93, 14.10; MALDI-TOF: *m/z* calculated for $[C_{104}H_{53}N_7O_{11}]^+$: 1575.380, found: 1575.323.

Ugi product 15: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (19.4 mg, 0.025 mmol), paraformaldehyde (1.2 mg, 0.03 mmol), 4,4'-(((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))dianiline (5 mg, 0.015 mmol) and *tert*-butyl isocyanide (3.4 µL, 0.03 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **15** (13.1 mg, 42 %) as a brown solid; R_f: 0.42 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 (d, *J* = 9.2 Hz, 4H), 6.97 (d, J = 9.3 Hz, 4H), 5.94 (s, 2H), 4.85 (s, 2H), 4.31 - 4.16 (m, 4H), 3.90 (dd, J = 5.6, 3.7 Hz, 4H), 3.76 (s, 4H). 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.02, 163.74, 148.22, 147.76, 146.01, 145.55, 145.43, 145.33, 145.29, 145.22, 145.17, 145.16, 145.08, 144.87, 144.75, 144.71, 144.62, 144.57, 144.56, 144.28, 143.94, 143.91, 143.86, 143.75, 143.65, 143.27, 143.21, 143.14, 143.07, 143.05, 143.01, 142.94, 142.91, 142.77, 142.58, 142.44, 142.38, 142.34, 142.19, 142.04, 141.63, 141.23, 141.12, 141.07, 140.86, 140.35, 136.49, 125.88, 114.52, 72.19, 70.93, 69.47, 68.13, 64.57, 51.84, 43.98, 28.76; MALDI-TOF: *m/z* calculated for $[C_{78}H_{32}N_2O_7]^+$: 2081.354, found: no molecular peak could be observed.

Ugi bis-product 29: The general procedure for the Ugi reaction was followed using using dicarboxylic acid **28b** (10.5 mg, 0.0125 mmol), paraformaldehyde (1.2 mg, 0.030 mmol), aniline (2.8 µL, 0.030 mmol) and *tert*-butyl isocyanide (3.4 µL, 0.030 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **29** (9.4 mg, 62 %) as a brown solid; R_f 0.55 (CH_2Cl_2/ethyl acetate: 7/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 - 7.73 (m, 4H), 7.55 - 7.50 (m, 4H), 7.41 (t, *J* = 7.4 Hz, 3H), 6.17 (s, 2H), 4.71 (s, 1H), 4.67 (s, 1H), 4.24 - 4.17 (m, 2H), 3.99 (s, 2H), 1.39 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.33, 164.35, 149.17, 149.06, 147.53, 147.20, 146.53, 146.09, 145.58, 145.51, 145.14, 144.96, 144.81, 144.76, 144.50, 144.30, 144.21, 143.98, 143.90, 143.70, 143.59, 143.47, 142.77, 141.78, 141.60, 141.36, 140.56, 130.27, 129.17, 128.07, 71.41, 68.67, 55.33, 51.61, 40.83, 29.70, 28.7; MALDI-TOF: *m/z* calculated for $[C_{88}H_{36}N_4O_4]^+$: 1212.273, found: 1212.236.

2.6.2.3 Synthesis of Passerini products

General procedure for the Passerini reaction: To a suspension of fullerenoacetic acid **1b** (0.0125 mmol, 1 equiv.) in dichloromethane (15 mL) was added the corresponding aldehyde (0.015 mmol, 1.2 equiv.), followed by the addition of the corresponding isocyanide (0.015 mmol, 1.2 equiv.). The reaction mixture was stirred for

48 h at room temperature, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel to afford the corresponding Passerini products.

Passerini product 16: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1.4 µL, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (*n*-hexane/CH_2Cl_2: 1/3) yielded **16** (10.5 mg, 90 %) as a brown solid. R_f 0.48 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.92 (s, 1H), 5.28 (d, *J* = 4.9 Hz, 1H), 4.91 (s, 1H), 2.55 - 2.40 (m, 1H), 1.38 (s, 9H), 1.13 (dd, *J* = 6.9, 4.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.49, 165.34, 147.92, 147.88, 145.49, 145.45, 145.30, 145.24, 145.18, 144.89, 144.76, 144.73, 144.69, 144.66, 144.59, 144.57, 143.90, 143.89, 143.75, 143.24, 143.12, 143.05, 142.93, 142.91, 142.41, 142.19, 142.09, 142.02, 141.94, 141.08, 140.32, 140.21, 136.45, 80.66, 70.33, 70.27, 67.08, 51.65, 39.09, 30.77, 28.71, 18.80, 17.56; MALDI-TOF: *m/z* calculated for $[C_{71}H_{19}NO_3]^+$: 933.136, found: 933.028.

Passerini product 17: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1.4 µL, 0.015 mmol), and cyclohexyl isocyanide (1.9 µL, 0.015 mmol). Isolation by column chromatography (*n*-hexane/CH_2Cl_2: 1/2) yielded **17** (9.6 mg, 84 %) as a brown solid; R_f 0.38 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.00 (d, *J* = 8.3 Hz, 1H), 5.39 (d, *J* = 4.6 Hz, 1H), 4.91 (s, 1H), 3.92 - 3.81 (m, 1H), 2.57 - 2.45 (m, 1H), 2.00 - 1.88 (m, 2H), 1.76 - 1.65 (m, 2H), 1.65 - 1.57 (m, 1H), 1.44 - 1.17 (m, 5H), 1.15 (d, *J* = 2.0 Hz, 3H), 1.13 (d, *J* = 2.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.35, 165.33, 147.94, 147.85, 145.50, 145.47, 145.45, 145.34, 145.32, 145.27, 145.20, 144.91, 144.78, 144.76, 144.72, 144.69, 144.60, 144.59, 144.57, 143.93, 143.77, 143.27, 143.17, 143.08, 143.05, 142.96, 142.93, 142.43, 142.21, 142.20, 142.11, 142.06, 142.00, 141.25, 141.23, 141.10, 140.34, 140.17, 136.49, 136.47, 80.38, 70.32, 70.28, 67.10, 48.16, 39.04, 33.16, 32.99, 30.81, 25.50, 24.81, 24.78, 18.88, 17.44; MALDI-TOF: *m/z* calculated for $[C_{73}H_{21}NO_3]^+$: 959.152, found: 959.062.

Passerini product 18: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1.4 µL, 0.015 mmol) and 1-isocyano-2-(2-methoxyethoxy)ethane **S8** (1.9 mg, 0.015 mmol). Isolation

by column chromatography (CH_2Cl_2/ethyl acetate: 9/1) yielded **18** (9.8 mg, 80 %) as a brown solid; R_f 0.67 (CH_2Cl_2/ethyl acetate: 7/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.69 (s, 1H), 5.34 (d, *J* = 4.8 Hz, 1H), 4.92 (s, 1H), 3.77 - 3.49 (m, 8H), 3.41 (s, 3H), 2.59 - 2.38 (m, 1H), 1.16 (dd, *J* = 6.9, 2.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.48, 165.38, 148.03, 147.91, 145.50, 145.45, 145.39, 145.28, 145.25, 145.22, 145.12, 144.99, 144.72, 144.70, 144.66, 144.65, 144.55, 144.51, 144.48, 143.94, 143.92, 143.74, 143.72, 143.26, 143.10, 143.04, 143.01, 142.98, 142.84, 142.39, 142.21, 142.09, 142.07, 142.05, 142.03, 141.16, 141.01, 140.98, 140.46, 140.43, 136.47, 136.42, 80.23, 71.90, 70.21, 69.71, 59.08, 39.11, 38.54, 30.88, 18.83, 17.50; MALDI-TOF: *m/z* calculated for $[C_{72}H_{21}NO_5]^+$: 979.142, found: 978.997.

Passerini product 19: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1.4 µL, 0.015 mmol) and benzyl isocyanide (1.8 µL, 0.015 mmol). Isolation by column chromatography (*n*-hexane/CH_2Cl_2: 1/2) yielded **19** (11.2 mg, 93 %) as a brown solid; R_f 0.45 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 - 7.30 (m, 5H), 6.46 (t, *J* = 5.4 Hz, 1H), 5.44 (d, *J* = 4.7 Hz, 1H), 4.87 (s, 1H), 4.58 - 4.51 (m, 2H), 1.17 (dd, *J* = 6.9, 1.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.49, 165.34, 147.92, 147.88, 145.49, 145.45, 145.30, 145.24, 145.18, 144.89, 144.76, 144.73, 144.69, 144.66, 144.59, 144.57, 143.90, 143.89, 143.75, 143.24, 143.12, 143.05, 142.93, 142.91, 142.41, 142.19, 142.09, 142.02, 141.94, 141.08, 140.32, 140.21, 136.45, 80.66, 70.33, 70.27, 67.08, 51.65, 39.09, 30.77, 28.71, 18.80, 17.56; MALDI-TOF: *m/z* calculated for $[C_{74}H_{17}NO_3]^+$: 967.954, found: 968.035.

Passerini product 20: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1.4 µL, 0.015 mmol) and *tert*-butyl (2-(2-(2-isocyanoethoxy)ethoxy)ethyl)carbamate **S7** (3.9 mg, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 9/1) yielded **20** (11.4 mg, 82 %) as a brown solid; R_f 0.50 (CH_2Cl_2/ethyl acetate: 7/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.65 (s, 1H), 5.33 (s, 1H), 4.98 (s, 1H), 4.93 (s, 1H), 3.67 - 3.51 (m, 10H), 3.41 - 3.23 (m, 2H), 2.54 - 2.43 (m, 1H), 1.45 (s, 9H), 1.16 (dd, *J* = 6.9, 5.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.54, 165.46, 155.94, 148.02, 145.46, 145.29, 145.27, 145.24, 145.22, 145.12, 144.99, 144.70, 144.68, 144.64, 144.56, 144.50, 144.47, 143.93, 143.92, 143.74, 143.72, 143.24, 143.10, 143.04, 143.00, 142.98, 142.84, 142.40, 142.20, 142.09, 142.07, 142.02, 141.99, 141.15, 140.96, 140.43,

136.49, 80.29, 70.34, 70.20, 69.72, 60.37, 40.37, 39.21, 38.56, 30.81, 28.46, 18.81; MALDI-TOF: *m/z* calculated for $[C_{78}H_{32}N_2O_7]^+$: 1108.221, found: 1108.120.

Passerini product 21: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), 3,6,9,12-tetraoxatridecanal (3.0 mg, 0.015 mmol) and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 9/1) yielded **21** (8.2 mg, 64 %) as a brown solid; R_f 0.45 (CH_2Cl_2/ethyl acetate: 7/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.31 (s, 1H), 5.55 (t, *J* = 4.5 Hz, 1H), 4.93 (s, 1H), 4.04 (d, *J* = 4.6 Hz, 2H), 3.81 - 3.62 (m, 10H), 3.58- 3.54 (m, 2H), 3.39 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.12, 165.02, 147.95, 145.51, 145.49, 145.29, 145.15, 144.95, 144.73, 144.67, 144.61, 144.56, 144.51, 143.92, 143.92, 143.75, 143.24, 143.23, 143.04, 143.02, 143.00, 142.87, 142.42, 142.10, 141.98, 141.75, 141.31, 141.18, 140.98, 140.90, 140.45, 138.75, 137.84, 136.47, 74.61, 71.93, 71.03, 70.62, 70.55, 70.49, 70.34, 70.27, 59.08, 51.71, 38.82, 29.70, 28.70; MALDI-TOF: *m/z* calculated for $[C_{76}H_{29}NO_7]^+$: 1067.194, found: 1067.081.

Passerini product 22: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), octanal (2.4 µL, 0.015 mmol) and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **22** (9.5 mg, 77 %) as a brown solid; R_f 0.65 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.98 (s, 1H), 5.40 (t, *J* = 5.7 Hz, 1H), 4.88 (s, 1H), 2.09 - 1.98 (m, 2H), 1.54 - 1.47 (m, 2H), 1.38 (s, 9H), 1.28 - 1.23(m, 8H) 0.90 - 0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.13, 165.20, 147.89, 145.48, 145.45, 145.31, 145.24, 145.18, 144.88, 144.76, 144.69, 144.66, 144.56, 143.92, 143.76, 143.23, 143.05, 143.02, 142.91, 142.41, 142.16, 142.09, 141.99, 141.23, 141.20, 141.06, 140.23, 140.20, 136.45, 136.43, 76.50, 70.35, 70.27, 51.59, 39.06, 32.10, 31.74, 29.70, 29.26, 29.13, 28.71, 25.03, 22.65, 14.12; MALDI-TOF: *m/z* calculated for $[C_{75}H_{27}NO_3]^+$: 989.199, found: 989.049.

Passerini product 23: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1.4 µL, 0.015 mmol) and 4-isocyano-1,1,3-trimethoxybutane (2.6 mg, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 9/1) yielded **23** (11.3 mg, 88 %) as a brown solid; R_f 0.37 (CH_2Cl_2/ethyl acetate: 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.55 -

6.44 (m, 1H), 5.36 (dd, *J* = 10.9, 4.7 Hz, 1H), 4.90 (s, 1H), 4.56 - 4.48 (m, 1H), 3.63 - 3.53 (m, 1H), 3.52 - 3.40 (m, 2H), 3.38 (d, *J* = 2.0 Hz, 3H), 3.36 - 3.34 (m, 6H), 2.55 - 2.44 (m, 1H), 1.93 - 1.83 (m, 1H), 1.81 - 1.72 (m, 1H), 1.17 (d, *J* = 6.9, 1.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.56, 168.52, 165.46, 165.45, 147.90, 145.48, 145.30, 145.28, 145.23, 145.14, 144.99, 144.94, 144.91, 144.73, 144.71, 144.69, 144.66, 144.64, 144.55, 144.51, 143.94, 143.92, 143.73, 143.25, 143.09, 143.04, 143.01, 142.99, 142.85, 142.39, 142.20, 142.08, 142.05, 142.00, 141.17, 140.44, 136.47, 101.84, 80.41, 76.10, 76.06, 70.22, 57.17, 57.14, 53.31, 53.26, 53.16, 53.15, 41.32, 38.56, 35.06, 34.99, 30.81, 30.78, 18.88, 18.86, 17.59, 17.51; MALDI-TOF: *m/z* calculated for $[C_{74}H_{25}NO_6]^+$: 1023.168, found: 1023.073.

Passerini product 24: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1 µL, 0.011 mmol) and methyl (2-isocyanoacetyl)-L-phenylalanyl-L-valinate **S9** (5.2 mg, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/methanol: 9/1) yielded **24** (6.72 mg, 55 %) as a brown solid; R_f 0.6 (CH_2Cl_2/methanol: 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 - 7.27 (m, 2H), 7.25 - 7.18 (m, 3H), 7.02 - 6.09 (m, 1H), 6.75 - 6.65 (m, 1H), 6.15 - 6.06 (m, 1H), 5.37 - 5.31 (m, 1H), 4.95 - 4.93 (m, 1H), 4.71 - 4.59 (m, 1H), 4.46 - 4.36 (m, 1H), 4.18 - 3.90 (m, 2H), 3.69 (s, 3H), 3.17 - 2.98 (m, 2H), 2.55 - 2.41 (m, 1H), 2.16 - 1.96 (m, 1H), 1.21 - 1.12 (m, 6H), 0.92 - 0.76 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.94, 168.92, 165.76, 159.88, 153.00, 152.80, 152.23, 148.09, 148.02, 147.42, 147.16, 145.52, 145.18, 145.15, 145.13, 145.11, 145.07, 145.05, 144.66, 144.64, 144.62, 144.55, 144.50, 144.39, 144.37, 144.31, 143.86, 143.85, 143.60, 143.17, 143.15, 143.12, 142.97, 142.90, 142.87, 142.82, 142.80, 142.33, 142.32, 142.16, 142.12, 142.03, 142.02, 141.60, 141.10, 141.09, 140.90, 140.88, 139.89, 139.06, 139.03, 136.27, 136.22, 123.20, 116.39, 115.03, 114.93, 114.79, 114.78, 114.53, 77.71, 72.85, 72.73, 66.49, 55.73, 55.68, 55.62, 55.48, 51.32, 50.65, 43.29, 31.07, 28.65, 28.63, 28.60, 26.78, 20.27, 19.73, 19.56, 17.49; MALDI-TOF: *m/z* calculated for $[C_{84}H_{33}N_3O_7]^+$: 1195.2319, found: 1195.025.

Passerini product 25: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), formaldehyde (37 % in water, 1.6 µL, 0.015 mmol) and methyl isocyanoacetate (1.4 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **25** (8.7 mg, 77 %) as a brown solid; R_f 0.73 (CH_2Cl_2/ethyl acetate: 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.86 (s, 1H), 5.00 (s, 2H),

4.90 (s, 1H), 4.21 (d, *J* = 5.2 Hz, 2H), 3.82 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.88, 166.28, 165.07, 147.74, 145.48, 145.32, 145.29, 145.24, 145.14, 145.10, 144.94, 144.77, 144.72, 144.70, 144.64, 144.56, 144.52, 143.95, 143.75, 143.28, 143.10, 143.04, 143.02, 142.85, 142.38, 142.20, 142.09, 142.03, 141.21, 141.04, 140.51, 136.53, 70.02, 64.07, 52.67, 40.97, 38.01, 29.68; MALDI-TOF: *m/z* calculated for $[C_{67}H_9NO_5]^+$: 907.048, found: 907.036.

Passerini product 26: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyraldehyde (1.4 µL, 0.015 mmol) and methyl 4-isocyanobutanoate **S1** (1.9 mg, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **26** (10.5 mg, 85 %) as a brown solid; R_f 0.70 (CH_2Cl_2/ethyl acetate: 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.74 (s, 1H), 5.39 (d, *J* = 4.4 Hz, 1H), 4.99 (s, 1H) 3.70 (s, 3H), 3.48 - 3.37 (m, 2H), 2.58 - 2.47 (m, 1H), 2.45 (t, *J* = 6.9 Hz, 2H), 1.96 - 1.85 (m, 2H), 1.15 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.27, 168.60, 165.38, 148.06, 147.95, 145.45, 145.41, 145.30, 145.28, 145.24, 145.16, 145.00, 144.96, 144.73, 144.66, 144.55, 144.51, 143.93, 143.75, 143.27, 143.13, 143.05, 143.01, 142.89, 142.41, 142.21, 142.09, 142.04, 141.19, 141.06, 141.03, 140.33, 136.46, 136.42, 80.14, 70.42, 70.34, 51.95, 39.19, 38.76, 31.82, 30.77, 29.69, 24.11, 18.89, 17.36; MALDI-TOF: *m/z* calculated for $[C_{72}H_{19}NO_5]^+$: 977.946, found: 977.601.

Passerini product 27: The general procedure for the Passerini reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), isobutyrlaldehyde (1.6 µL, 0.015 mmol), and isocyanide **S5** (1.4 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **27** (8.2 mg, 70 %) as a brown solid; R_f 0.7 (CH_2Cl_2/ethyl acetate: 8/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.58 (d, *J* = 7.3 Hz, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 8.41 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 5.50 (d, *J* = 4.2 Hz, 1H), 4.99 (s, 1H), 4.25 - 4.18 (m, 2H), 3.71 - 3.61 (m, 1H), 3.54 - 3.44 (m, 1H), 3.10 (s, 6H), 2.63 - 2.50 (m, 1H), 1.86 (p, *J* = 7.1 Hz, 2H), 1.70 (p, *J* = 6.5 Hz, 2H), 1.20 (dd, *J* = 6.9, 4.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.66, 165.48, 164.72, 164.20, 157.20, 147.93, 147.58, 145.34, 145.24, 145.19, 145.17, 145.10, 145.08, 145.06, 144.99, 144.88, 144.62, 144.58, 144.55, 144.51, 144.49, 144.35, 144.33, 144.21, 144.15, 143.78, 143.59, 143.48, 143.14, 143.07, 142.91, 142.85, 142.82, 142.78, 142.67, 142.54, 142.09, 142.06, 141.94, 141.92, 141.87, 141.84, 141.80, 140.96, 140.91, 140.86, 140.68, 140.46, 140.40, 136.21, 135.98, 132.95, 131.52, 131.25,

130.36, 125.31, 124.97, 122.99, 114.72, 113.38, 80.33, 70.39, 70.23, 44.79, 39.13, 38.73, 38.36, 30.89, 29.70, 25.57, 25.49, 21.07, 19.01, 17.42; MALDI-TOF: *m/z* calculated for $[C_{86}H_{30}N_2O_5]^+$: 1170.215, found: 1171.258.

Passerini bis-product 30: The general procedure for the Passerini reaction was followed using dicarboxylic acid **28b** (12.5, 0.015 mmol), isobutyraldehyde (2.8 µL, 0.030 mmol) and cyclohexyl isocyanide (3.8 mg, 0.030 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 9/1) yielded **30** (5.8 mg, 65 %) as a brown solid; R_f 0.33 (CH_2Cl_2/ethyl acetate: 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.07 (d, *J* = 8.1 Hz, 1H), 5.46 (d, *J* = 4.7 Hz, 1H), 4.98 (s, 1H), 3.99 - 3.88 (m, 1H), 2.64 - 2.51 (m, 1H), 2.07 - 1.95 (m, 2H), 1.82 - 1.92 (m, 2H), 1.71 - 1.65 (m, 1H), 1.51 - 1.28 (m, 5H), 1.21 (dd, J = 6.9, 1.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.29, 165.01, 149.20, 148.81, 147.45, 147.42, 147.40, 146.40, 146.19, 145.83, 145.79, 145.75, 145.67, 145.64, 145.35, 145.32, 145.10, 144.97, 144.95, 144.86, 144.58, 144.44, 144.40, 144.30, 144.27, 144.25, 144.22, 143.92, 143.73, 143.62, 141.72, 141.71, 80.64, 70.11, 67.69, 48.26, 33.02, 30.61, 29.69, 24.81, 18.65, 17.71, 17.26; MALDI-TOF: *m/z* calculated for $[C_{86}H_{42}N_2O_6]^+$: 1198.304, found: 1198.365.

2.6.3 Steady-state photolysis

Photobleaching of DPBF was used for monitoring generation of singlet oxygen ($^1O_2$) in toluene medium, produced by the photosensitizer. Solutions containing DPBF (20 µM) and photosensitizer **4**, **5**, **6**, **9** and **16** (10 µM) were photolysed in 1 cm path length quartz cells (3 mL) with monochromatic laser light with a wavelength of 660 nm from 30 mW (Thera Lase - DMC, São Carlos, SP, Brazil). The laser was positioned 1 cm from the sample to be irradiated. The kinetic of photooxidation of DPBF, due to its reaction with $^1O_2$ was monitored spectrophotometrically (Varian CARY 50-BIO spectrometer) by following the decrease in the absorbance at 415 nm for DPBF. Measurements were carried out in triplicate and performed at room temperature (25.0 ± 0.1 ºC). The constant rate was determined by using a first-order kinetic model which gives a better fit to the experimental data due to higher correlation coefficient (R^2 close to 1).

2.7 References

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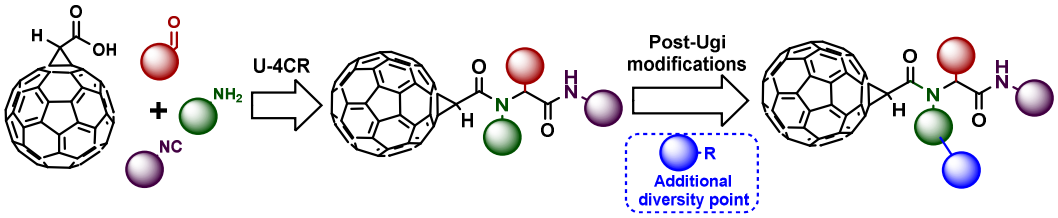
Chapter 3

Ugi reaction as a tool for the synthesis of complex fullerene C_{60} derivatives

Abstract



In order to increase complexity and expand the realm of transformations for fullerenes derivatives, we report an improved approach to modify this class of compounds through the Ugi reaction, using substituted anilines as the amino component. This strategy gives us an extra diversification point which can be used as precursor of more complex post-Ugi products.

3.1 Introduction

The functionalization of fullerenes and carbon nanomaterials is a key topic for the development of novel products of interest in the biological, medical, and material science fields.[1-5] Although these compounds have already been used in a great number of applications,[6-11] more complex derivatives are always required from industry and academia in order to explore all of its potential.

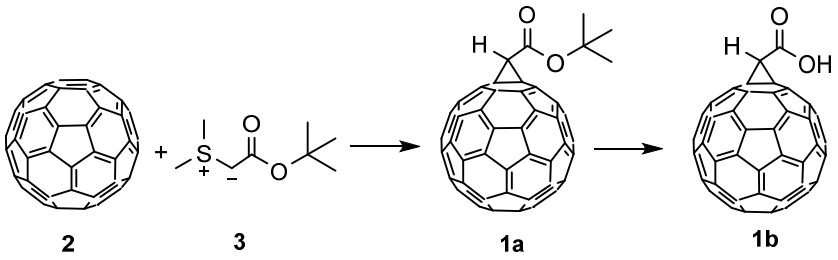
With the limited reaction types that can be performed on fullerene C_{60} and the great versatility of multicomponent reactions, being able to add many diversity points in a single step, it can be envisioned that both may be ideal "partners", presenting a new protocol for the functionalization of fullerenes.[12-14] In the previous chapter, we could effectively decorate fullerene C_{60} *via* the Ugi and Passerini reaction in a simple method and under mild conditions, whereas the biggest limitation was the necessary use of anilines as the amino component for the Ugi reaction. Since the product complexity obtained with this methodology is remarkably high and diverse derivatives could be easily produced, we aim to improve the scope of this protocol by applying modified anilines as the amino component.

3.2 Synthetic strategy

The construction of new fullereno derivatives *via* Ugi reaction is based on the use of functional handles linked in the amino component (aniline). Further modifications can be performed without affecting the already existing peptoid backbone of the first generation derivatives, thereby increasing product complexity by subsequent reactions and expanding the scope of possible transformations.

3.3 Synthesis of fullereno-Ugi derivatives

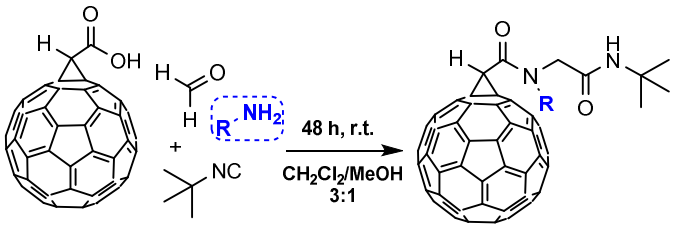
We started our studies applying the same protocol reported and optimized in the previous chapter, where we could successfully functionalize fullerenes *via* the Ugi-4CR. Like our prior report, the carboxylic acid component (**1b**) is fixed as the source of the fullerene cage and can be easily produced *via* the Wilson method (Scheme 1).[15]



Scheme 1. Synthesis of carboxylated fullerene.

All Ugi four-component reactions were performed in a 3:1 mixture of dichloromethane/methanol as the solvent at room temperature and stirred for 48 hours. Since the scope of the aldehyde and isocyanide components had been previously established, we focus our efforts in analyzing the scope of the amino component for this reaction applying a set of different amines (Table 1).

Table 1. Scope elucidation of the Ugi reaction with fullerenoacetic acid.



Product	Amino component (R)	Yield (%)	Product	Amino component (R)	Yield (%)
4	Methylamine	-	**18**	*N*-Boc-*p*-Phenylenediamine	85
5	*tert*-Butylamine	-	**19**	*N*-Fmoc-*p*-Phenylenediamine	68
6	Cyclohexylamine	-	**20**	4-Ethynylaniline	80
7	Propargylamine	-	**21**	4-Vinylaniline	82
8	Aniline	93	**22**	4-Aminoacetophenone	69
9	4-Methoxyaniline	96	**23**	Ethyl-4-aminobenzoate	75
10	4-Nitroaniline	-	**24**	Ethyl (4-aminophenyl)acetate	82
11	4-Iodoaniline	77	**25**	*N*-(2,4-Dinitrophenyl)-1,4-phenylenediamine	74
12	4-Bromoaniline	82	**26**	Phenyl hydrazine	-
13	4-Chloroaniline	80	**27**	Ethyl hydrazinoacetate	-
14	4-Fluoroaniline	85	**28**	*N*-*tert*-Butoxy carbonylglycyl hydrazide	-
15	2-Bromoaniline	60	**29**	2-Aminopyridine	-
16	4-Aminophenol	95	**30**	3-Aminopyridine	-
17	4-(2-Aminoethyl)aniline	89	**31**	4-Aminopyridine	-

As depicted in Table 1, all aliphatic amines tested (**4** - **7**) as well as hidrazines (**26**, **27**), hydrazide (**28**), and pyridines (**29** - **31**) failed to yield the product, although most of the anilines evaluated gave the products in good yields (**8** - **25**). Electron withdrawing groups (EWG) linked to the aniline had a negative effect on the reaction (**11**, **20** and **22**), and in some cases no product could be observed (**10**), an expected result due to the nucleophilic character necessary for the amino component to react in the Ugi reaction. In parallel, electron donating groups (EDG) furnished products with high yields and good conversion rates (**9**, **16**, and **17**). In general, we could observe the same trend for our previous report where only anilines derivatives were able to form the products. Such selectivity can be highlighted in compound **17**, which is only susceptible to the U-4CR in the aromatic position, while the aliphatic amino group remains unreactive.

Exploring this methodology, fifteen new fullereno-Ugi derivatives could be synthesized (Figure 1), displaying a variety of groups attached to the product structure. Products **11** to **15** contain halogen atoms that were able to undergo coupling reactions to further modify these compounds. Similarly, the hydroxyl and amino functionalities in compounds **16** to **19** make them suitable for follow-up reactions. Unsaturated products which can participate in metathesis, coupling or click reactions are represented in examples **20** and **21**, followed by carbonyl compounds **22**, **23** and **24**, that offer a different route for derivatization. Finally, compound **25** includes the dye Disperse yellow 9 in its structure, demonstrating the diversity generated by this protocol. This library of assorted products open the possibility to perform most of the known classic organic reactions, expanding the number of fullereno derivatives and increasing the complexity of the final product.

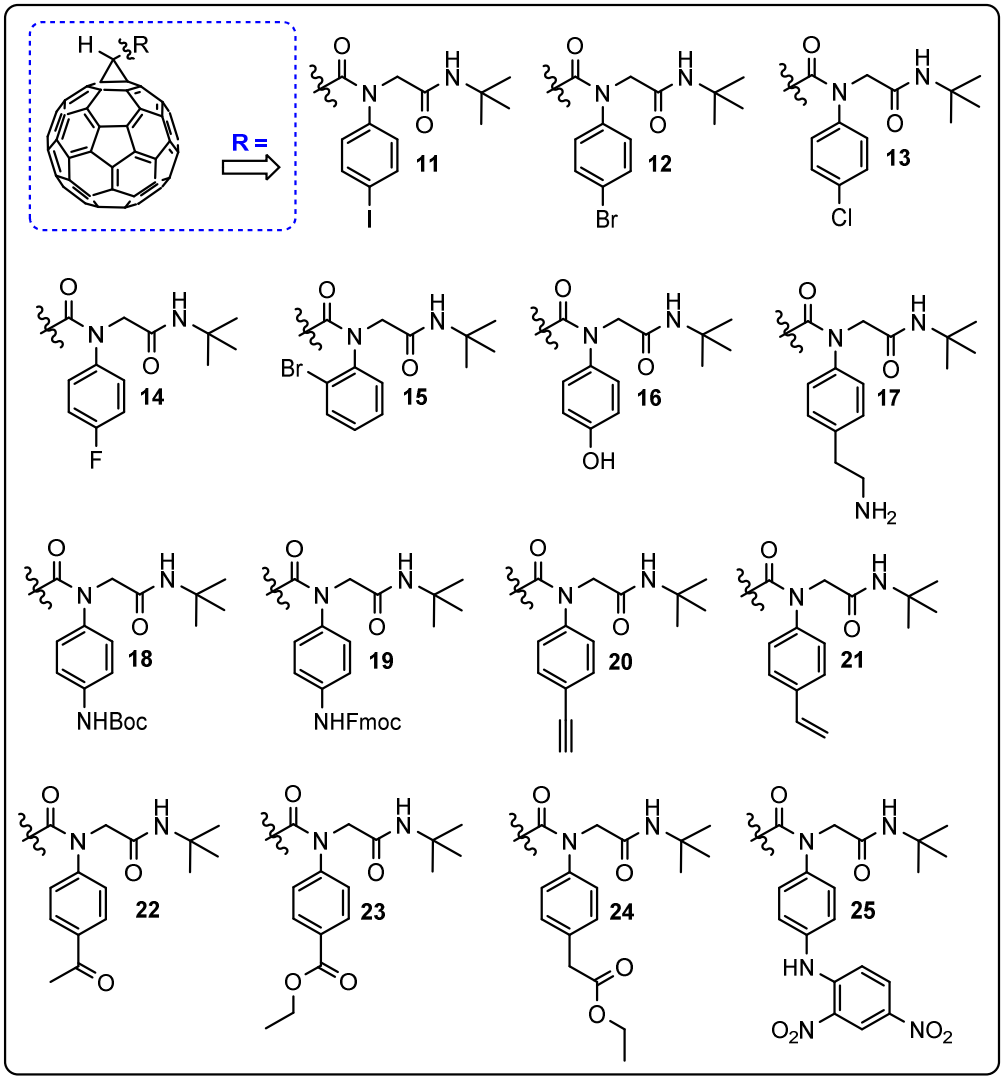
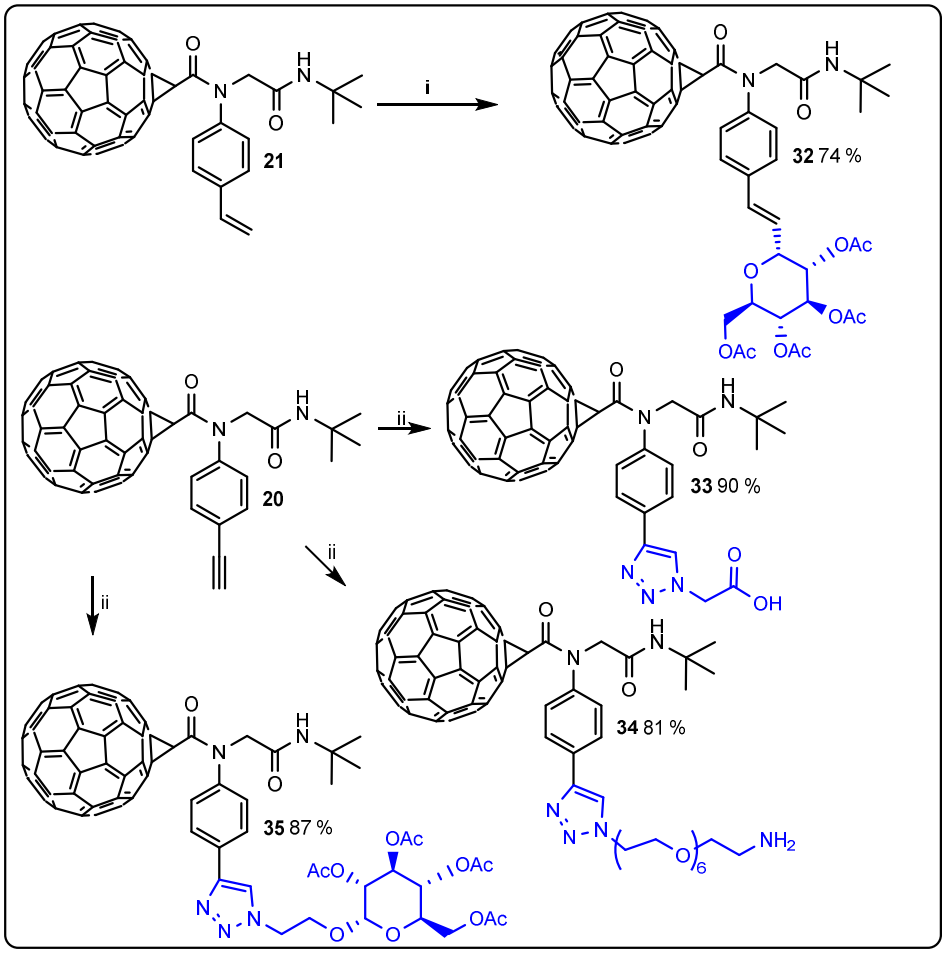


Figure 1. Fullereno-Ugi derivatives synthesized.

3.4 Post-Ugi reaction modifications

For selected products, post-Ugi modifications were performed as a proof of concept, demonstrating that subsequent reactions are possible and very feasible (Scheme 2). We started by performing a palladium catalyzed coupling reaction (Heck reaction) between derivative alkene **21** and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, obtaining product **32** with 74 % of yield. The copper-catalyzed Huisgen cycloaddition reaction was also evaluated, where the derivatization of alkyne **20** with three different azides (2-azidoacetic acid, *O*-(2-aminoethyl)-*O*′-(2-azidoethyl) pentaethylene glycol and (2*R*,4*R*,5*S*,6*S*)-2-(acetoxymethyl)-6-(2-azidoethoxy) tetrahydro-2*H*-pyran-3,4,5-triyl triacetate) gave products **33**, **34** and **35** with 90, 81 and

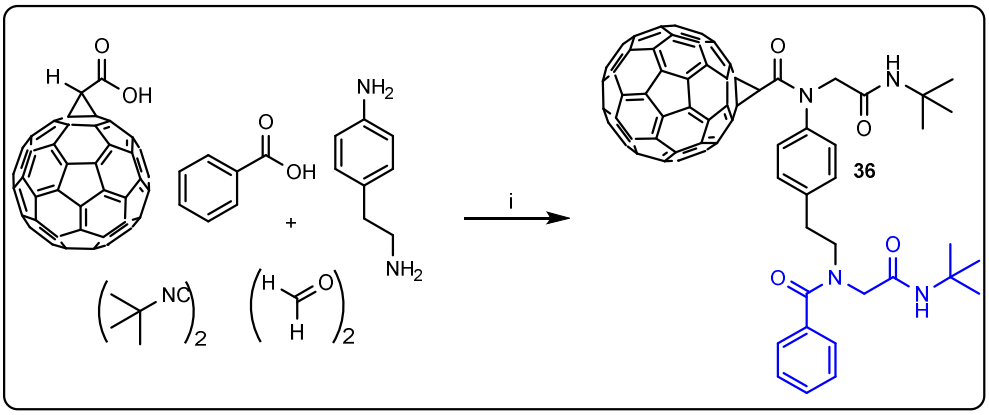
87 % of yield, respectively. All post-Ugi modifications proceeded smoothly and under mild reaction conditions, while illustrating few of the possible transformations that can be achieved employing modified anilines as substrates.



Scheme 2. Post Ugi modification of products: i) **21**, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, potassium carbonate, palladium (II) acetate, THF, DMF, 80 °C, 18 h; ii) **20**, corresponding azide, sodium ascorbate, copper (II) acetate, THF, H_2O, r.t., 24 h.

To conclude our experiments, a one pot 7-component reaction (Scheme 3) was performed, exploiting the different behaviour of aliphatic and aromatic amines in the classic U-4CR and in this protocol. Fullerenoacetic acid **1b**, benzoic acid, 4-(2-aminoethyl)aniline, paraformaldehyde (2 equiv.) and *tert*-butyl isocyanide (2 equiv.) were mixed together in a round bottom flask under the optimized reaction conditions and stirred for 48 h to furnish compound **36** as the major product. With a yield of 84 %

and 97 % yield for each individual bond-forming process, this reaction highlights the potential of the developed methodology.



Scheme 3. 7-component reaction; i) CH_2Cl_2/MeOH 3:1, r.t., 48 h.

3.5 Conclusion

With the results obtained in this chapter we could effectively increase the scope for the functionalization of fullerene C_{60} *via* the Ugi reaction. The protocol previously reported could be improved and, with the use of substituted anilines, subsequent reactions can be performed to expand the library of fullereno-Ugi derivatives, offering a new alternative for the synthesis of more complex products.

3.6 Experimental Part

3.6.1 General information

All commercial reagents were used without further purification. Column chromatography was carried out using Merck silica gel 60 (0.040 - 0.063 mm) and analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 aluminium sheets. Proton and carbon nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were recorded at 25 °C in the respective solvents on an Agilent DD2 400 NMR spectrometer at 399.917 and 100.570 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to TMS (^{1}H NMR) and to residual solvent signal (^{13}C NMR). High resolution mass spectra were obtained from an Orbitrap Elite mass spectrometer (Thermofisher Scientific, Bremen, Germany) equipped with an HESI electrospray ion source (spray voltage 4.0 kV; capillary temperature 275 °C, source heater temperature

40 °C; FTMS resolution 60.000). Electrospray ionization mass spectra (ESI-MS) were recorded on a API 3200 system, Triple Quadrupole MS (AB Sciex) equipped with ESI electrospray ion source (positive spray voltage 5.5 kV, negative spray voltage 4.5 kV, and source heater temperature 400 °C). MALDI-TOF mass spectra were acquired on a Bruker Ultraflex III-MALDI-TOF/TOF mass spectrometer (Bruker Daltonics, Bremen, Germany). The samples solubilized in toluene (0.5 µL) were mixed with the equal volume of a 0.1 % w/v *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrilein acetone (DCTB, matrix) on a stainless steel target and dried under air. The analysis was performed in a reflector positive ion mode, using the source and reflector voltages of 25 and 26.3 kV, respectively. Desorption/ionization of the analytes was achieved by a YAG 354 nm laser.

3.6.2 Synthesis

3.6.2.1 Synthesis of starting materials

***tert*-Butyl [60]fullerenoacetate (1a):** To a toluene solution (100 mL) of fullerene C_{60} (144 mg, 0.2 mmol) was added dropwise a toluene solution (5 mL) of *tert*-butyl (dimethylsulfanylidene)acetate (33 mg, 0.19 mmol) at room temperature under nitrogen atmosphere. After stirring for 18 h the reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography in silica gel to afford the product **1a**. Brown solid; Yield 55 %; MALDI-TOF: *m/z* calculated for $[C_{66}H_{10}O_2]^+$: 834.068, found: 834.257.

[60]Fullerenoacetic acid (1b): A toluene solution (50 mL) of *tert*-butyl [60]fullereno acetate **1a** (84 mg, 0.11 mmol) and *p*-TsOH.H_2O (42 mg, 0.25 mmol) was refluxed for 8 h to afford a suspension. The precipitate was filtrated and washed with toluene (50 mL) and water (20 mL). The solid was dissolved in a 1:1 mixture of dichloromethane and dioxane (30mL) and filtered again. The filtrate was concentrated under reduced pressure to afford the product **1b**. Dark brown solid; Yield: 80 %; MALDI-TOF: *m/z* calculated for $[C_{62}H_2O_2]^+$: 778.055, found: 778.128.

3.6.2.2 Synthesis of fullereno-Ugi products

General procedure for the Ugi reaction: Paraformaldehyde (1 equiv.) and corresponding amines (1.2 equiv.) were added to a round bottom flask containing methanol (5 mL / 0.01 mmol) and stirred for 2 hours at room temperature. This recently formed imine was added to a suspension of fullerenoacetic acid **1b** (1.0 equiv.) in dichloromethane (15 mL / 0.01 mmol) followed by the addition of *tert*-butyl isocyanide (1.2 equiv.). The reaction mixture was stirred for 48 hours, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel to afford the corresponding Ugi products.

Ugi product 8: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), aniline (1.4 µL, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **8** (11.2 mg, 93 %) as a brown solid; R_f 0.20 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 7.9 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 6.21 (s, 1H), 4.61 (s, 1H), 4.46 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.20, 164.87, 147.89, 146.95, 145.53, 145.20, 145.17, 145.08, 144.68, 144.64, 144.59, 144.49, 144.43, 144.35, 143.87, 143.62, 143.20, 143.12, 142.98, 142.92, 142.88, 142.81, 142.31, 142.20, 142.18, 142.03, 141.71, 141.11, 140.93, 139.22, 136.31, 130.46, 129.36, 128.00, 72.44, 55.46, 51.62, 41.96, 28.74; MALDI-TOF: *m/z* calculated for $[C_{74}H_{18}N_2O_2]^+$: 966.137, found: 966.041.

Ugi product 9: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 4-methoxyaniline (1.9 mg, 0.015 mmol) and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **9** (11.9 mg, 96 %) as a brown solid; R_f 0.15 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 - 7.64 (m, 2H), 7.10 - 7.04 (m, 2H), 6.19 (s, 1H), 4.62 (s, 1H), 4.42 (s, 2H), 3.85 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.33, 165.21, 159.92, 147.99, 147.00, 145.53, 145.20, 145.16, 145.09, 145.07, 144.68, 144.64, 144.58, 144.43, 144.34, 143.88, 143.62, 143.20, 143.12, 142.98, 142.92, 142.89, 142.81, 142.33, 142.20, 142.18, 142.03, 141.12, 140.93, 139.32, 136.35, 134.36, 129.15, 115.54, 72.51, 55.67, 51.57, 41.83, 28.73; MALDI-TOF: *m/z* calculated for $[C_{75}H_{20}N_2O_3]^+$: 996.147, found: 996.045.

Ugi product 11: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 4-iodoaniline (3.3 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **11** (10.5 mg, 77 %) as a brown solid; R_f 0.95 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 6.06 (s, 1H), 4.59 (s, 1H), 4.41 (s, 2H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.89, 164.60, 147.66, 146.70, 145.44, 145.22, 145.18, 145.12, 145.09, 144.99, 144.68, 144.66, 144.64, 144.62, 144.51, 144.51, 144.38, 143.88, 143.64, 143.20, 143.12, 143.00, 142.93, 142.91, 142.83, 142.33, 142.17, 142.16, 142.05, 141.55, 141.19, 140.94, 139.57, 139.39, 136.46, 129.90, 94.80, 72.17, 55.19, 51.74, 41.48, 28.74, 28.72; MALDI-TOF: *m/z* calculated for $[C_{74}H_{17}IN_2O_2]^+$: 1092.033, found: 1091.907.

Ugi product 12: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 4-bromoaniline (2.6 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **12** (10.7 mg, 82 %) as a brown solid; R_f 0.90 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 - 7.60 (m, 4H), 6.06 (s, 1H), 4.59 (s, 1H), 4.41 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.89, 164.63, 147.66, 146.71, 145.43, 145.22, 145.18, 145.12, 145.09, 144.98, 144.68, 144.66, 144.65, 144.62, 144.51, 144.38, 143.88, 143.64, 143.20, 143.13, 143.00, 142.93, 142.91, 142.84, 142.33, 142.17, 142.16, 142.05, 141.19, 140.95, 140.85, 139.37, 136.45, 133.59, 129.76, 123.27, 72.17, 55.21, 51.75, 41.52, 28.74; MALDI-TOF: *m/z* calculated for $[C_{74}H_{17}BrN_2O_2 + Na]^+$: 1069.035, found: 1069.179.

Ugi product 13: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 4-chloroaniline (1.9 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **13** (10.0 mg, 80 %) as a brown solid; R_f 0.87 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 6.06 (s, 1H), 4.58 (s, 1H), 4.41 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.92, 164.70, 152.81, 147.66, 146.72, 145.85, 145.43, 145.22, 145.18, 145.12, 145.09, 144.98, 144.68, 144.66, 144.62, 144.50, 144.38, 143.88, 143.64, 143.21, 143.13, 143.00, 142.93, 142.91, 142.83,

142.32, 142.17, 142.05, 141.19, 140.95, 140.32, 139.35, 136.44, 135.24, 130.60, 129.47, 129.18, 128.93, 72.18, 55.27, 51.75, 41.56, 28.74; MALDI-TOF: *m/z* calculated for $[C_{74}H_{17}ClN_2O_2]^+$: 1000.098, found: 1000.145.

Ugi product 14: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 4-fluoroaniline (1.4 µL, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **14** (10.45 mg, 85 %) as a brown solid; R_f 0.80 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 - 7.74 (m, 2H), 7.30 - 7.26 (m, 2H), 6.09 (s, 1H), 4.58 (s, 1H), 4.41 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.02, 164.86, 147.72, 146.81, 145.44, 145.23, 145.19, 145.11, 145.10, 144.99, 144.69, 144.67, 144.65, 144.62, 144.51, 144.49, 144.38, 143.88, 143.64, 143.21, 143.14, 143.01, 142.94, 142.84, 142.33, 142.19, 142.18, 142.05, 141.19, 140.97, 139.26, 136.39, 130.10, 130.02, 117.54, 117.31, 72.27, 55.41, 51.72, 41.75, 28.74; MALDI-TOF: *m/z* calculated for $[C_{74}H_{17}FN_2O_2$+ Na$]^+$: 1007.116, found: 1007.274

Ugi product 15: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 2-bromoaniline (1.7 µL, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **15** (8.5 mg, 65 %) as a brown solid; R_f 0.77 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 7.7 Hz, 1H), 7.61 - 7.55 (m, 2H), 7.52 - 7.46 (m, 1H), 6.20 (s, 1H), 4.61 (s, 1H), 4.46 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.20, 164.87, 147.89, 146.95, 145.53, 145.22, 145.17, 145.10, 145.08, 144.68, 144.67, 144.59, 144.49, 144.43, 144.35, 143.87, 143.62, 143.37, 143.20, 142.98, 142.92, 142.88, 142.81, 142.31, 142.21, 142.18, 142.03, 141.71, 141.11, 140.93, 139.55, 139.22, 136.31, 130.46, 129.37, 128.00, 72.44, 55.47, 51.63, 41.96, 28.74; MALDI-TOF: *m/z* calculated for $[C_{74}H_{17}BrN_2O_2$ + Na$]^+$: 1069.035, found: 1069.281.

Ugi product 16: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 4-aminophenol (1.6 µL, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 8/2) yielded **16** (11.6 mg, 95 %) as a brown solid; R_f 0.15 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400

MHz, $CDCl_3$) δ = 7.50 - 7.40 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.54 (bs, 1H), 6.68 (s, 1H), 4.61 (s, 1H), 4.48 (s, 2H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.18, 165.50, 156.72, 147.90, 146.93, 145.51, 145.20, 145.17, 145.09, 145.06, 144.67, 144.66, 144.60, 144.54, 144.45, 144.36, 143.88, 143.64, 143.18, 143.13, 142.99, 142.93, 142.90, 142.84, 142.81, 142.68, 142.36, 142.17, 142.15, 142.05, 141.97, 141.21, 141.16, 140.94, 140.19, 139.27, 136.38, 129.08, 124.57, 117.12, 72.43, 55.70, 51.76, 41.72, 28.69; MALDI-TOF: *m/z* calculated for $[C_{74}H_{18}N_2O_3]^+$: 982.132, found: 982.337.

Ugi product 17: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 4-(2-aminoethyl)aniline (2.0 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 8/2) yielded **17** (11.2 mg, 89 %) as a brown solid; R_f 0.12 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.15 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 6.35 (s, 1H), 4.28 - 4.18 (m, 5H), 3.12 (t, *J* = 6.7 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.83, 165.19, 147.87, 146.92, 145.73, 145.47, 145.25, 145.19, 145.16, 145.12, 144.71, 144.66, 144.61, 144.58, 144.54, 144.38, 143.87, 143.68, 143.18, 143.15, 143.02, 142.96, 142.81, 142.43, 142.20, 142.18, 142.04, 141.10, 140.98, 138.90, 136.42, 130.07, 127.54, 115.85, 71.91, 52.36, 52.20, 51.45, 40.50, 34.11, 28.66; MALDI-TOF: *m/z* calculated for $[C_{76}H_{23}N_3O_2 + Na]^+$: 1032.168, found: 1032.227.

Ugi product 18: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), *N*-Boc-*p*-phenylenediamine (3.1 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 19/1) yielded **18** (11.5 mg, 85 %) as a brown solid; R_f 0.37 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 6.64 (s, 1H), 6.14 (s, 1H), 4.62 (s, 1H), 4.42 (s, 2H), 1.52 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.19, 165.08, 153.14, 148.36, 147.94, 146.94, 145.53, 145.20, 145.16, 145.07, 145.06, 144.68, 144.63, 144.58, 144.53, 144.44, 144.34, 143.88, 143.65, 143.63, 143.21, 143.11, 142.91, 142.81, 142.33, 142.19, 142.03, 141.14, 140.93, 139.41, 139.26, 136.41, 136.17, 128.65, 122.57, 72.43, 60.37, 51.03, 41.70, 28.73, 28.29; MALDI-TOF: *m/z* calculated for $[C_{79}H_{27}N_3O_4]^+$: 1082.200, found: 1082.185.

Ugi product 19: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), *N*-Fmoc-*p*-phenylenediamine (5 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2/ethyl acetate: 19/1) yielded **19** (10.2 mg, 68 %) as a brown solid; R_f 0.38 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 7.5 Hz, 2H), 7.66 - 7.59 (m, 4H), 7.58 - 7.55 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.33 (td, *J* = 7.5, 1.2 Hz, 2H), 6.99 (s, 1H), 6.18 (s, 1H), 4.62 - 4.57 (m, 3H), 4.39 (s, 2H), 4.27 (t, *J* = 6.3 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.33, 165.06, 153.10, 147.86, 146.90, 145.50, 145.21, 145.17, 145.08, 145.06, 144.68, 144.64, 144.60, 144.51, 144.46, 144.36, 143.89, 143.63, 143.55, 143.21, 143.13, 142.99, 142.92, 142.89, 142.82, 142.33, 142.18, 142.04, 141.39, 141.16, 140.94, 139.35, 138.68, 136.53, 136.41, 128.69, 127.87, 127.17, 124.84, 120.10, 72.40, 66.91, 55.47, 51.65, 47.09, 41.72, 28.74; MALDI-TOF: *m/z* calculated for $[C_{89}H_{29}N_3O_4 + Na]^+$: 1226.205, found: 1226.217.

Ugi product 20: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 4-ethynylaniline (1.7 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **20** (9.9 mg, 80 %) as a brown solid; R_f 0.87 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 6.08 (s, 1H), 4.59 (s, 1H), 4.43 (s, 2H), 3.19 (s, 1H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.93, 164.68, 147.71, 146.75, 145.48, 145.23, 145.19, 145.12, 145.10, 145.02, 144.69, 144.67, 144.63, 144.51, 144.39, 143.89, 143.66, 143.22, 143.13, 143.00, 142.94, 142.91, 142.84, 142.34, 142.19, 142.06, 141.96, 141.19, 140.96, 139.38, 136.45, 134.11, 128.08, 123.29, 82.34, 79.27, 72.22, 55.25, 51.75, 41.63, 29.70, 28.75; MALDI-TOF: *m/z* calculated for $[C_{76}H_{18}N_2O_2]^+$: 990.137, found: 990.075.

Ugi product 21: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 4-vinylaniline (1.7 µL, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **21** (10.1 mg, 82 %) as a brown solid; R_f 0.85 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5, 2H), 6.76 (dd, *J* = 17.6, 10.8 Hz, 1H), 6.17 (s, 1H), 5.82 (d, *J* = 17.5 Hz, 1H), 5.36 (d, *J* = 11.0 Hz, 1H), 4.63 (s, 1H), 4.44 (s, 2H), 1.40 (s,

9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.15, 164.90, 147.87, 146.87, 145.52, 145.20, 145.16, 145.08, 145.06, 144.67, 144.63, 144.59, 144.50, 144.45, 144.35, 143.88, 143.62, 143.20, 143.11, 142.98, 142.91, 142.88, 142.81, 142.31, 142.18, 142.03, 141.12, 140.92, 140.91, 139.39, 138.54, 136.39, 135.51, 128.06, 115.91, 72.36, 55.41, 51.63, 41.68, 28.74; MALDI-TOF: *m/z* calculated for $[C_{76}H_{20}N_2O_2]^+$: 992.152, found: 991.947.

Ugi product 22: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), 4-aminoacetophenone (2 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **22** (8.7 mg, 69 %) as a brown solid; R_f 0.57 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 2H), 6.07 (s, 1H), 4.60 (s, 1H), 4.45 (s, 2H), 2.65 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.38, 166.81, 164.53, 150.98, 147.59, 146.62, 145.82, 145.42, 145.24, 145.20, 145.13, 145.11, 144.96, 144.70, 144.67, 144.65, 144.53, 144.48, 144.41, 143.89, 143.64, 143.22, 143.14, 143.01, 142.94, 142.91, 142.83, 142.30, 142.18, 142.05, 141.19, 140.97, 139.41, 136.43, 130.41, 128.24, 127.98, 72.10, 55.15, 51.81, 41.52, 28.75, 26.82; MALDI-TOF: *m/z* calculated for $[C_{76}H_{20}N_2O_3]^+$: 1008.147, found: 1008.166.

Ugi product 23: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), ethyl-4-aminobenzoate (2.5 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **23** (9.7 mg, 75 %) as a brown solid; R_f 0.57 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 6.06 (s, 1H), 4.59 (s, 1H), 4.45 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.40 (s, 9H), 1.35 - 1.32 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.65, 165.45, 164.56, 147.63, 146.64, 145.62, 145.45, 145.22, 145.19, 145.11, 145.09, 144.99, 144.68, 144.65, 144.62, 144.51, 144.49, 144.39, 143.89, 143.63, 143.21, 143.12, 142.99, 142.92, 142.89, 142.82, 142.29, 142.17, 142.16, 142.04, 141.18, 140.96, 139.43, 137.84, 136.42, 131.70, 127.97, 113.54, 72.11, 61.52, 55.16, 51.78, 41.52, 28.74, 14.31; MALDI-TOF: *m/z* calculated for $[C_{77}H_{22}N_2O_4 + Na]^+$: 1061.147, found: 1061.354.

Ugi product 24: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), ethyl (4-aminophenyl)acetate (2.7 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **24** (10.8 mg, 82 %) as a brown solid; R_f 0.60 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 6.16 (s, 1H), 4.63 (s, 1H), 4.44 (s, 2H), 4.18 - 4.09 (m, 2H), 3.68 (s, 2H), 1.40 (s, 9H), 1.24 - 1.20 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.78, 167.14, 164.85, 147.87, 146.93, 145.52, 145.19, 145.16, 145.08, 145.06, 144.67, 144.62, 144.58, 144.48, 144.41, 144.34, 143.86, 143.61, 143.19, 143.10, 142.97, 142.91, 142.87, 142.79, 142.29, 142.19, 142.17, 142.02, 141.09, 140.92, 140.63, 139.24, 136.34, 135.49, 131.29, 131.29, 129.98, 128.07, 72.40, 61.12, 55.35, 51.63, 41.82, 41.01, 28.73, 14.19; MALDI-TOF: *m/z* calculated for $[C_{78}H_{24}N_2O_4 + Na]^+$: 1075.162, found: 1075.350.

Ugi product 25: The general procedure for the Ugi reaction was followed using fullerenoacetic acid **1b** (9.7 mg, 0.0125 mmol), paraformaldehyde (0.5 mg, 0.0125 mmol), *N*-(2,4-dinitrophenyl)-1,4-phenylenediamine (4.1 mg, 0.015 mmol), and *tert*-butyl isocyanide (1.7 µL, 0.015 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **25** (10.6 mg, 74 %) as a brown solid; R_f 0.77 (CH_2Cl_2/ethyl acetate: 19/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.00 (s, 1H), 9.18 (d, *J* = 2.7 Hz, 1H), 8.13 (dd, *J* = 9.5, 2.7 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 9.4 Hz, 1H), 6.15 (s, 1H), 4.68 (s, 1H), 4.47 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.97, 164.57, 147.53, 146.71, 146.18, 145.32, 145.28, 145.23, 145.17, 145.15, 144.90, 144.74, 144.71, 144.66, 144.59, 144.50, 144.44, 144.42, 143.87, 143.64, 143.25, 143.21, 143.09, 143.03, 143.01, 142.83, 142.31, 142.23, 142.17, 142.04, 141.22, 141.03, 140.66, 139.01, 138.09, 137.65, 136.39, 131.82, 130.18, 130.02, 126.79, 124.04, 115.82, 72.28, 55.31, 51.83, 42.03, 28.76; MALDI-TOF: *m/z* calculated for $[C_{80}H_{21}N_5O_6]^+$: 1147.149, found: 1047.264.

3.6.2.3 Synthesis of post-Ugi products

Product 32: Fullereno-Ugi product **21** (5 mg, 0.005 mmol) was added to a Schlenk flask under nitrogen atmosphere and solubilized with THF (2 mL), followed by the addition of potassium carbonate (1 mg, 0.005 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2.5 mg, 0.006 mmol) solubilized in DMF (1 mL). Palladium

acetate (0.1 mg, 0.0005 mmol) was added and the mixture was stirred for 18 hours at 80 °C. The solvent was evaporated under reduced pressure and the crude product was purified by recrystalization with THF and pentane to yield product **32** (4.8 mg, 74 %) as a brown solid; MALDI-TOF: *m/z* calculated for $[C_{92}H_{42}N_2O_{12} + Na]^+$: 1345.236, found: 1345.372.

Product 33: To a mixture of fullereno-Ugi product **20** (5 mg, 0.005 mmol) and 2-azidoacetic acid (0.45 µL, 0.006 mmol) in a closed Schlenk flask, dissolved in a solution of H_2O/THF (2 mL, 1:1), were added copper (II) acetate (0.1 mg, 0.0005 mmol) and sodium ascorbate (0.1 mg, 0.0005 mmol). The reaction mixture was stirred for 24 hours at room temperature, after which THF was evaporated under reduced pressure. Water (5 mL) was added and the crude product was filtered in a nitrocellulose acetate membrane. The product was purified by recrystalization with THF and pentane to yield product **33** (4.9 mg, 90 %) as a brown solid; MALDI-TOF: *m/z* calculated for $[C_{78}H_{21}N_5O_4]^+$: 1091.159, found: 1091.442.

Product 34: To a mixture of fullereno-Ugi product **20** (5 mg, 0.005 mmol) and *O*-(2-Aminoethyl)-*O'*-(2-azidoethyl)pentaethylene glycol (2.1 mg, 0.006 mmol) in a closed Schlenk flask, dissolved in a solution of H_2O/THF (2 mL, 1:1), were added copper (II) acetate (0.1 mg, 0.0005 mmol) and sodium ascorbate (0.1 mg, 0.0005 mmol). The reaction mixture was stirred for 24 hours at room temperature, after which THF was evaporated under reduced pressure. Water (5 mL) was added and the crude product was filtered in a nitrocellulose acetate membrane. The product was purified by recrystalization with THF and pentane to yield product **34** (5.4 mg, 81 %) as a brown solid; MALDI-TOF: *m/z* calculated for $[C_{88}H_{44}N_6O_7 + Na]^+$: 1319.327, found: 1319.203.

Product 35: To a mixture of fullereno-Ugi product **20** (5 mg, 0.005 mmol) and (2*R*,4*R*,5*S*,6*S*)-2-(acetoxymethyl)-6-(2-azidoethoxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (2.5 mg, 0.006 mmol) in a closed Schlenk flask, dissolved in a solution of H_2O/THF (2 mL, 1:1), were added copper (II) acetate (0.1 mg, 0.0005 mmol) and sodium ascorbate (0.1 mg, 0.0005 mmol). The reaction mixture was stirred for 24 hours at room temperature, after which THF was evaporated under reduced pressure. Water (5 mL) was added and the crude product was filtered in a nitrocellulose acetate membrane. The product was purified by recrystalization with THF and pentane to yield

product **35** (6.1 mg, 87 %) as a brown solid; MALDI-TOF: *m/z* calculated for $[C_{92}H_{41}N_5O_{12} + Na]^+$: 1430.264, found: 1430.028.

Product 36: Paraformaldehyde (0.5 mg, 0.013 mmol, 2.6 equiv.) and 4-(2-aminoethyl)aniline (0.8 mg, 0.006 mmol, 1.2 equiv.) were added to a round bottom flask containing methanol (3 mL) and the mixture was stirred for 2 hours at room temperature. The recently formed imine was added to a suspension of fullerenoacetic acid **1b** (4 mg 0.0125 mmol, 1.0 equiv.) in dichloromethane (9 mL) followed by the addition of *tert*-butyl isocyanide (1.6 µL, 0.013 mmol, 2.6 equiv.) and benzoic acid (0.6 mg 0.005 mmol, 1.0 equiv.), respectively. The reaction mixture was stirred for 48 hours, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (CH_2Cl_2/ethyl acetate: 8/2) on silica gel to afford product **36** (5.1 mg, 84 %) as a brown solid; MALDI-TOF: *m/z* calculated for $[C_{89}H_{38}N_4O_4 + Na]^+$: 1249.278, found: 1249.439.

3.7 References

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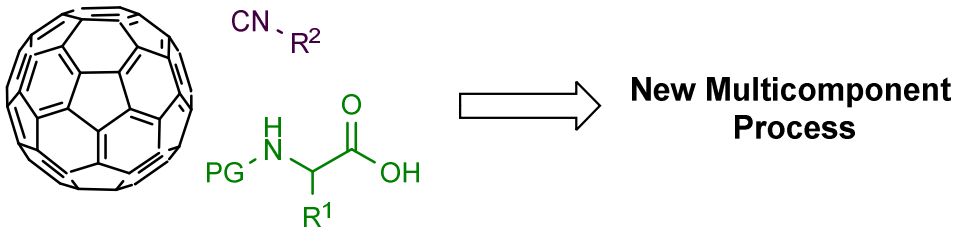
Chapter 4

Development of a new multicomponent reaction to achieve unique fullerene scaffolds

Abstract



In this chapter we report a novel isocyaned-based multicomponent reaction between fullerene C_{60}, a *N*-protected amino acid, and an isocyanide. This protocol generates a complex and unusual heterocyclic product scaffold with good yields, under mild reaction conditions in a single step, adding a new page in the handbook for chemical decoration of fullerenes.

4.1 Introduction

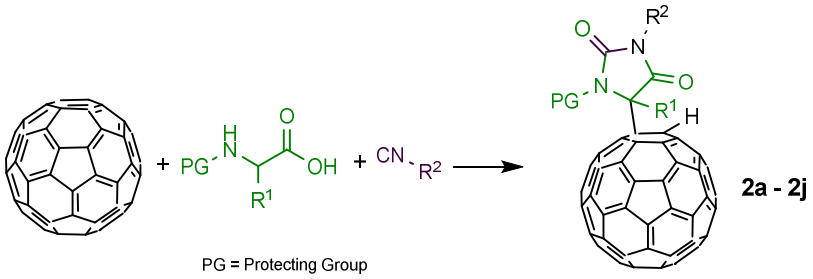
Since their discovery, fullerenes have been extensively studied for their physical, electronic, medical and biochemical properties.[1-7] As mentioned in the previous chapters, this "gold rush" resulted in many findings and applications developed in the past decades,[8-14] and now, after 30 years of research, the number of new publications describing protocols to derivatize fullerenes is critically declining. Considering that most of the known classic organic and inorganic reactions have been already evaluated in fullerene chemistry,[15] in order to continue to expand the number of fullerene transformations, innovative synthetic procedures are required.

Isocyanides are compounds with a unique reactivity that are able to participate in a large number of organic reactions.[16-18] The divalent carbon on the isocyanide structure can act both as nucleophile and electrophile, making this class of compounds valuable assets in synthetic chemistry. Although a reaction between isocyanides and fullerene C_{60} has been previously reported,[19] no MCR directly involving these two classes of compounds has been described.

Similarly, amino acids and peptides have been studied since the early stages of modern chemistry, being the cornerstone for many organic reactions due to the presence of an amino and a carboxylic acid group in its structure.[20-22] They are cheap, stable, reactive, chiral and biologically relevant building blocks,[22-24] whose combination with isocyanides can provide a new way to decorate fullerenes. Taking this into consideration, we conceptualize the development of a new isocyanide-based multicomponent reaction involving fullerene C_{60}, isocyanides and *N*-protected amino acids in order to broaden the spectrum of fullerene reactions and to offer a new route for the derivatization of this class of compounds.

4.2 Synthetic Strategy

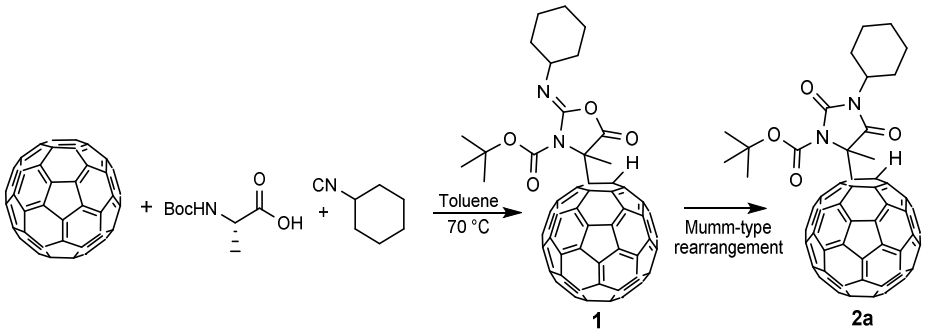
As synthetic strategy, we aim to explore the distinct reactivity of isocyanides in combination with fullerene C_{60} and *N*-protected amino acids. The ambiphilic character of the isocyanide component allows the formation of the heterocycle directly linked to the fullerene structure, affording products with the atypical scaffold demonstrated in Scheme 1.



Scheme 1. Proposed IMCR with fullerene C_{60}, *N*-protected amino acids, and isocyanides.

4.3 Synthesis of IMCRs products

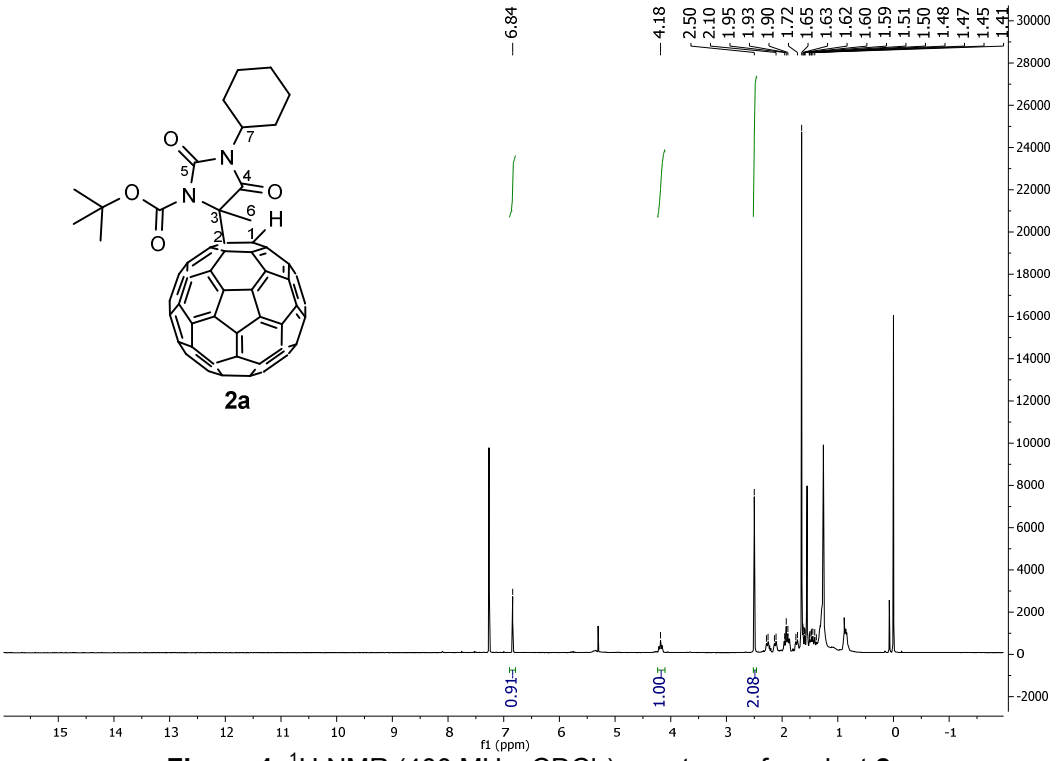
In a model experiment for this IMCR, fullerene C_{60}, Boc-L-alanine and cyclohexyl isocyanide were combined in toluene at room temperature, and the progress of the reaction was followed by TLC. After 8 hours and no product formation, the temperature was raised to 70 °C and the reaction mixture stirred for further 15 hours. TLC analysis showed the formation of a single product that after purification was analysed by proton and carbon NMR and its proposed structure is shown in Scheme 2.



Scheme 2. Model experiment for this protocol.

It is our believe that first, intermediate **1** is formed, followed by a Mumm-type rearrangement that leads to the final product **2a**. This assumption is corroborated by a recent literature report from Liang and co-workers in which the same type of rearrangement as above is described for the isocyanide insertion to cyclic oximes.[25] Further evidence of the product structure was obtained by NMR, where chemical shifts analysis demonstrate a more fitting pattern for the structure **2a** in comparison to structure **1** (Figure 1). It is apparent that the ligation point to the fullerene is the α-carbon center of the amino acid (3), considering that the NMR spectra revealed a quaternary center (disappearance of the α-proton signal), and the adjacent protons of the methyl residue (6) showed no coupling, appearing as a singlet at 2.50 ppm. The

presence of a singlet at 6.84 ppm also sugests the direct linkage of a proton (1) to the fullerene structure. Furthermore, a small coupling between the α-proton of the isocyanide (7, 4.18 ppm) and the α-carbon of the amino acid (3) in the 2D heteronuclear multiple bond correlation spectrum offer additional proof of the product structure.



2a

Figure 1. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of product **2a**.

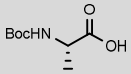
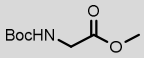
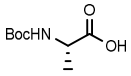
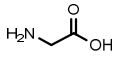
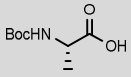
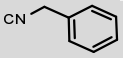
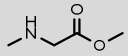
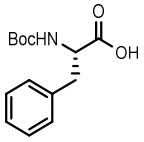
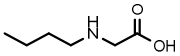
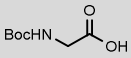
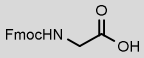
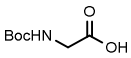
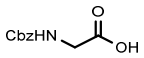
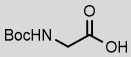
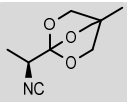
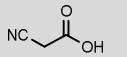
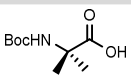
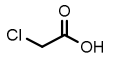
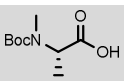
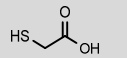
Optimization of the solvent, temperature and reaction time were carried out using the same reactants as above. Different types of aromatic, aliphatic, polar, apolar and halogenated solvents were evaluated, and chlorobenzene was preferred, mainly due to the better solubility of C_{60}. During reaction time optimization it became clear that prolonged reaction times were not necessary, selecting finally 8 hours as the optimal reaction time. Temperature variation has a high effect on this process, considering that at room temperature the reaction did not proceed, even at longer reaction times and, at 60 °C, only a small amount of the product was isolated. In the temperature of 80 °C the highest yield was obtained, since higher temperatures led to the formation of multi-addition adducts, noticeably reducing the yields.

Table 1. Solvent, time and temperature optimization.

Solvent	Time (h)	Temp. (°C)	Yield (%)	Solvent	Time (h)	Temp. (°C)	Yield (%)
Dichloromethane	10	70	traces	Chlorobenzene	8	70	56
Toluene	10	70	47	Chlorobenzene	24	70	54
Chlorobenzene	10	70	56	Chlorobenzene	8	r.t.	--
n-Hexane	10	70	--	Chlorobenzene	8	60	10
Carbon disulfide	10	70	24	Chlorobenzene	8	80	64
Chlorobenzene	4	70	31	Chlorobenzene	8	90	60
Chlorobenzene	6	70	48	Chlorobenzene	8	100	53

In order to better understand the reaction and to confirm the proposed product structure, the scope of this new process was evaluated. Different *N*-protected amino acids (or equivalent compounds) and isocyanides were screened applying the optimized reaction condition (Table 2).

Table 2. Reagents screening for the multicomponent process.

Entry	*N*-protected AA or equivalent	Isocyanide	Yield (%)	Prod.	Entry	*N*-protected AA or equivalent	Isocyanide	Yield (%)	Prod.
1			64	**2a**	10			--	--
2			65	**2b**	11			--	--
3			45	**2c**	12			--	--
4			33	**2d**	13			--	--
5			74	**2e**	14			59	**2h**[a]
6			67	**2f**	15			63	**2i**
7			52	**2g**	16			--	--
8			--	--	17			--	--
9			--	--	18			68	**2j**

[a] Reaction was completed after 12 hours.

Entries 1, 2, 3, and 7 demonstrate that the isocyanide can be varied easily, although more bulky substrates furnish products with slight lower yields (e.g., entry 3). Similarly, steric hindred amino acids lowered yields (entry 4), while the use of Boc-glycine (AA without side chain) contributed to the highest yield (74 %) in this screening (entry 5).

Entry 8 illustrate the necessity of a proton connected to the α-carbon, since the use of α-aminoisobutyric acid yielded no product. The use of *N*-methylated Boc-glycine in entry 9 prevented the product formation, also demonstrating the requirement of this proton for the multicomponent process. Likewise, when amino acid esters were tested (entry 10) no reaction was observed, indicating that the carboxylic acid of the amino acid must be free for the process to occur.

Starting from unprotected amino acid (entry 11) did not yield the product, suggesting that an acidic proton linked to the nitrogen atom is required. This assumption was confirmed in entries 12 and 13, with the use of more basic amino derivatives such as sarcosine and *N*-butylglycine, which led to no product formation. Other carbamate protecting groups could be applied successfully (entries 14 and 15), despite the longer reaction time required for the Fmoc group. This result can be attributed to the lower solubility of this amino acid in the reaction solvent. Alternative compounds for the amino acid component were also evaluated. Nitriles or halogens groups proved inefficient (entries 16 and 17), albeit the use of thiogycolyc acid (entry 18) provided the product with excellent yields.

In total, ten derivatives (Figure 2) could be synthesized with good yields ranging from 33 to 74 %, establishing a new protocol for the decoration of fullerenes.

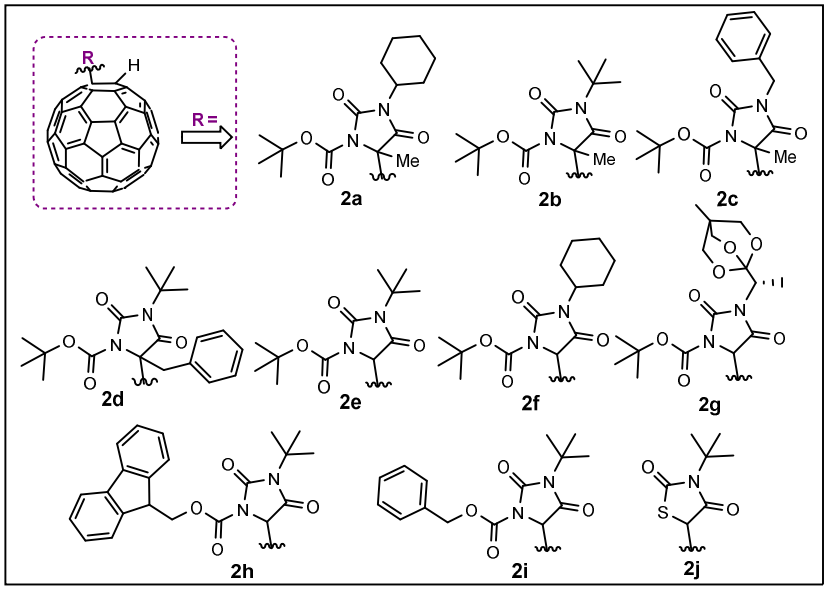


Figure 2. Structure of the synthesized products.

4.4 Conclusion

With the combination of fullerene C_{60}, amino acids, and isocyanides, ten different products containing a unique scaffold were synthesized. These compounds were obtained *via* a newly described multicomponent reaction that can aid in the search for new fullereno derivatives, while also laying the foundations for the development of novel multicomponent process involving fullerenes. Follow up studies will be carried out to further understand the reaction mechanism, better determine the scope of this process and comfirm the identity of the isolated products.

4.5 Experimental Part

4.5.1 General information

All commercial reagents were used without further purification. Column chromatography was carried out using Merck silica gel 60 (0.040 - 0.063 mm) and analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 aluminium sheets. Proton and carbon nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were recorded at 25 °C in the respective solvents on an Agilent DD2 400 NMR spectrometer at 399.917 and 100.570 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to TMS (^{1}H NMR) and to residual solvent signal (^{13}C NMR).

4.5.2 Synthesis

General procedure: In a two neck round bottom flask under nitrogen atmosphere, fullerene C_{60} (1 equiv.) was solubilized in chlorobenzene (30 mL / mmol). The amino acid or corresponding component (1 equiv.) was added next, followed by the addition of the isocyanide (1 equiv.), and the reaction was stirred for 8 hours at 80 °C. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using dichloromethane as eluent.

Product 2a: The general procedure was followed using fullerene C_{60} (36 mg, 0.05 mmol), Boc-L-alanine (9.5 mg, 0.05 mmol), and cyclohexyl isocyanide (6.2 µL, 0.05 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **2a** (28.4 mg, 57 %) as a brown solid; R_f 0.48 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.84 (s, 1H), 4.18 (tt, *J* = 11.7, 3.6 Hz, 1H), 2.50 (s, 3H), 2.33 - 2.18 (m, 1H), 2.17 - 2.07 (m, 1H), 2.00 - 1.83 (m,

3H), 1.80 - 1.69 (m, 1H), 1.65 (s, 9H), 1.63 - 1.57 (m, 1H), 1.52 - 1.36 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.85, 153.18, 151.72, 150.74, 150.42, 149.93, 147.24, 147.22, 146.88, 146.45, 146.34, 146.17, 146.13, 146.02, 145.90, 145.70, 145.69, 145.61, 145.59, 145.56, 145.44, 145.40, 145.36, 145.11, 144.64, 144.30, 144.29, 143.09, 143.03, 142.98, 142.80, 142.78, 142.71, 142.37, 142.29, 142.24, 142.19, 142.17, 142.06, 142.01, 142.00, 141.77, 141.65, 140.18, 140.02, 139.85, 138.58, 138.18, 138.00, 137.27, 83.10, 78.02, 77.42, 53.67, 32.72, 32.26, 28.32, 25.73, 25.44, 25.33, 14.94.

Product 2b: The general procedure was followed using fullerene C_{60} (36 mg, 0.05 mmol), Boc-L-alanine (9.5 mg, 0.05 mmol), and *tert*-butyl isocyanide (6 µL, 0.05 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **2b** (31.7 mg, 64 %) as a brown solid; R_f 0.52 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.01 (s, 1H), 2.45 (s, 3H), 1.74 (s, 9H), 1.66 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.86, 153.80, 151.97, 150.87, 150.43, 150.13, 147.24, 147.21, 146.97, 146.45, 146.44, 146.32, 146.31, 146.18, 146.13, 146.11, 146.01, 145.86, 145.69, 145.68, 145.66, 145.62, 145.53, 145.44, 145.42, 145.40, 145.39, 145.36, 145.16, 144.68, 144.31, 144.28, 143.03, 142.92, 142.80, 142.77, 142.75, 142.69, 142.40, 142.29, 142.17, 142.16, 142.05, 142.03, 142.01, 141.78, 141.77, 141.64, 140.23, 140.18, 140.00, 139.81, 139.08, 138.27, 138.09, 137.20, 83.12, 79.42, 77.75, 76.39, 55.92, 28.83, 28.30, 15.22.

Product 2c: The general procedure was followed using fullerene C_{60} (36 mg, 0.05 mmol), Boc-L-alanine (9.5 mg, 0.05 mmol), and benzyl isocyanide (6 µL, 0.05 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **2c** (23 mg, 45 %) as a brown solid; R_f 0.50 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 7.1 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.43 - 7.37 (m, 1H), 6.64 (s, 1H), 5.44 (d, *J* = 15.2, 1H), 4.55 (d, *J* = 15.2 Hz, 1H), 2.59 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.70, 152.79, 151.10, 150.42, 149.57, 148.67, 147.32, 147.22, 146.73, 146.46, 146.42, 146.40, 146.33, 146.17, 146.14, 146.03, 145.96, 145.69, 145.67, 145.64, 145.59, 145.56, 145.49, 145.46, 145.43, 145.40, 145.38, 145.02, 144.56, 144.29, 144.23, 143.09, 143.06, 143.00, 142.81, 142.80, 142.78, 142.73, 142.37, 142.33, 142.18, 142.15, 142.13, 142.02, 142.01, 141.98, 141.80, 141.78, 140.23, 140.20, 140.12, 139.90, 138.47, 137.93, 137.28, 135.46, 129.14, 128.71, 128.38, 83.04, 79.23, 47.38, 28.11.

Product 2d: The general procedure was followed using fullerene C_{60} (36 mg, 0.05 mmol), Boc-L-phenylalanine (8.5 mg, 0.05 mmol), and *tert*-butyl isocyanide (6 µL, 0.05 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **2d** (17.6 mg, 33 %) as a brown solid; R_f 0.75 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.38 - 7.33 (m, 1H), 7.08 (s, 1H), 4.11 - 4.02 (m, 2H), 1.75 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.58, 155.76, 153.45, 152.51, 151.67, 149.26, 148.54, 147.11, 147.04, 146.43, 146.28, 146.18, 146.14, 146.07, 145.83, 145.80, 145.73, 145.67, 145.62, 145.42, 145.39, 145.31, 145.21, 145.12, 144.92, 144.44, 144.24, 143.13, 143.11, 143.08, 143.03, 142.98, 142.95, 142.94, 142.91, 142.75, 142.74, 142.66, 142.30, 142.21, 142.17, 142.16, 142.09, 142.08, 142.03, 141.25, 141.20, 141.02, 139.98, 139.27, 136.28, 136.26, 132.30, 130.89, 128.82, 128.01, 83.26, 78.20, 77.42, 56.41, 54.64, 29.69, 29.65.

Product 2e: The general procedure was followed using fullerene C_{60} (36 mg, 0.05 mmol), Boc-glycine (8.5 mg, 0.05 mmol), and *tert*-butyl isocyanide (6 µL, 0.05 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **2e** (36.1 mg, 74 %) as a brown solid; R_f 0.45 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.92 (s, 1H), 5.72 (s, 1H), 1.73 (s, 9H), 1.69 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.54, 152.96, 150.21, 149.93, 149.78, 147.29, 147.26, 146.55, 146.50, 146.45, 146.37, 146.36, 146.24, 146.17, 146.07, 145.77, 145.74, 145.67, 145.65, 145.60, 145.50, 145.45, 145.43, 145.22, 144.96, 144.74, 144.37, 144.32, 144.27, 143.02, 142.96, 142.81, 142.75, 142.70, 142.39, 142.29, 142.27, 142.19, 142.16, 142.15, 142.13, 142.06, 142.01, 141.93, 141.79, 141.75, 140.28, 140.24, 140.16, 140.03, 139.34, 138.49, 138.42, 137.59, 83.59, 81.38, 74.05, 71.38, 55.81, 28.95, 28.27.

Product 2f: The general procedure was followed using fullerene C_{60} (36 mg, 0.05 mmol), Boc-glycine (8.5 mg, 0.05 mmol), and cyclohexyl isocyanide (6.2 µL, 0.05 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **2f** (33.6 mg, 67 %) as a brown solid; R_f 0.45 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.76 (s, 1H), 5.82 (s, 1H), 4.16 (tt, *J* = 11.8, 3.8 Hz, 1H), 2.22 (d, *J* = 11.9 Hz, 1H), 2.15 - 2.06 (m, 1H), 2.00 - 1.83 (m, 3H), 1.78 - 1.69 (m, 1H), 1.67 (s, 9H), 1.64 - 1.59 (m, 1H), 1.55 - 1.45 (m, 2H), 1.45 - 1.38 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.42, 152.76, 150.08, 149.75, 149.59, 147.28, 147.25, 146.48, 146.46, 146.44, 146.36, 146.36, 146.21, 146.18, 146.15, 146.06, 145.77, 145.71, 145.68, 145.64, 145.60, 145.47, 145.45, 145.43, 145.41, 145.15, 144.94, 144.69, 144.35, 144.29, 144.26, 143.07, 142.99, 142.80, 142.79,

142.75, 142.69, 142.32, 142.26, 142.23, 142.16, 142.14, 142.13, 142.05, 141.99, 141.93, 141.92, 141.77, 140.29, 140.17, 140.14, 140.03, 138.82, 138.43, 138.37, 137.61, 83.57, 79.84, 73.13, 53.19, 32.92, 32.46, 28.26, 25.73, 25.40, 25.26.

Product 2g: The general procedure was followed using fullerene C_{60} (36 mg, 0.05 mmol), Boc-glycine (8.5 mg, 0.05 mmol), and (S)-1-(1-isocyanoethyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (9 mg, 0.05 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **2g** (28 mg, 52 %) as a brown solid; R_f 0.17 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.02 (s, 1H), 5.84 (s, 1H), 4.72 (q, *J* = 7.2 Hz, 1H), 4.14 - 4.00 (m, 6H), 1.66 (s, 9H), 1.40 (d, *J* = 7.1 Hz, 3H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.28, 153.05, 150.75, 150.38, 149.60, 147.29, 147.23, 147.21, 146.71, 146.43, 146.39, 146.35, 146.25, 146.11, 146.04, 145.85, 145.80, 145.69, 145.55, 145.48, 145.43, 145.33, 145.16, 144.93, 144.90, 144.67, 144.42, 144.32, 144.25, 143.08, 143.03, 142.99, 142.93, 142.84, 142.75, 142.72, 142.66, 142.59, 142.42, 142.24, 142.15, 142.10, 142.08, 142.06, 141.99, 141.87, 141.76, 141.70, 140.29, 140.10, 140.00, 139.26, 138.96, 138.15, 137.32, 107.83, 83.11, 78.40, 72.86, 71.73, 53.63, 51.26, 30.20, 28.45, 16.23, 14.47.

Product 2h: The general procedure was followed using fullerene C_{60} (36 mg, 0.05 mmol), Fmoc-glycine (8.5 mg, 0.05 mmol), *tert*-butyl isocyanide (6 µL, 0.05 mmol), and 12 hours as reaction time. Isolation by column chromatography (CH_2Cl_2) yielded **2h** (32.4 mg, 59 %) as a brown solid; R_f 0.53 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (dd, *J* = 10.3, 7.5 Hz, 2H), 7.71 (t, *J* = 7.6 Hz, 2H), 7.46 - 7.37 (m, 2H), 7.37 - 7.29 (m, 2H), 6.86 (s, 1H), 5.81 (s, 1H), 4.82 (s, 1H), 4.76 - 4.69 (m, 1H), 4.44 (t, *J* = 6.5 Hz, 1H), 1.66 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.02, 152.62, 149.88, 149.51, 149.42, 147.31, 147.27, 146.52, 146.48, 146.39, 146.25, 146.20, 146.09, 145.82, 145.74, 145.69, 145.63, 145.52, 145.48, 145.46, 145.36, 145.18, 144.80, 144.72, 144.35, 144.30, 144.25, 143.29, 143.19, 143.03, 142.97, 142.83, 142.77, 142.73, 142.36, 142.30, 142.27, 142.19, 142.14, 142.08, 142.01, 141.97, 141.79, 141.77, 141.44, 141.39, 140.34, 140.28, 140.19, 140.05, 139.31, 138.54, 138.06, 137.27, 129.68, 128.59, 128.02, 127.99, 127.34, 127.31, 126.40, 124.95, 120.22, 120.14, 80.41, 73.20, 71.54, 68.62, 56.08, 47.06, 28.95.

Product 2i: The general procedure was followed using fullerene C_{60} (36 mg, 0.05 mmol), Cbz-glycine (8.5 mg, 0.05 mmol), and *tert*-butyl isocyanide (6 µL, 0.05 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **2i** (31.8 mg, 63 %) as a brown solid; R_f 0.55 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 - 7.49 (m, 2H), 7.47 - 7.39 (m, 3H), 6.98 (s, 1H), 5.86 (s, 1H), 5.43 (m, 2H), 1.66 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.11, 152.63, 149.84, 149.66, 149.51, 147.29, 147.25, 146.51, 146.47, 146.43, 146.37, 146.35, 146.24, 146.17, 146.07, 145.79, 145.74, 145.63, 145.55, 145.52, 145.50, 145.45, 145.43, 145.36, 145.18, 144.82, 144.70, 144.34, 144.27, 144.23, 143.08, 142.98, 142.95, 142.81, 142.75, 142.70, 142.36, 142.26, 142.19, 142.14, 142.05, 142.00, 141.94, 141.78, 141.73, 140.29, 140.25, 140.14, 140.03, 139.32, 138.48, 138.19, 137.32, 135.14, 129.68, 128.81, 128.58, 126.40, 80.95, 73.55, 68.92, 58.89, 56.03, 28.90.

Product 2j: The general procedure was followed using fullerene C_{60} (36 mg, 0.05 mmol), thioglycolic acid (3.5 µL, 0.05 mmol), and *tert*-butyl isocyanide (6 µL, 0.05 mmol). Isolation by column chromatography (CH_2Cl_2) yielded **2j** (30.3 mg, 68 %) as a brown solid; R_f 0.80 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.53 (d, *J* = 2.3 Hz, 1H), 5.31 (d, *J* = 2.3 Hz, 1H), 1.74 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.91, 154.05, 152.25, 151.38, 147.38, 147.32, 146.53, 146.50, 146.44, 146.39, 146.22, 146.21, 146.17, 146.11, 146.03, 145.71, 145.68, 145.61, 145.51, 145.49, 145.48, 145.46, 145.32, 145.04, 145.01, 144.78, 144.57, 144.44, 144.36, 144.27, 143.07, 142.99, 142.95, 142.84, 142.83, 142.75, 142.70, 142.34, 142.24, 142.21, 142.14, 142.12, 142.12, 141.96, 141.75, 141.70, 140.28, 140.10, 140.00, 139.84, 139.37, 138.66, 138.12, 137.99, 80.63, 73.63, 67.70, 57.21, 28.95.

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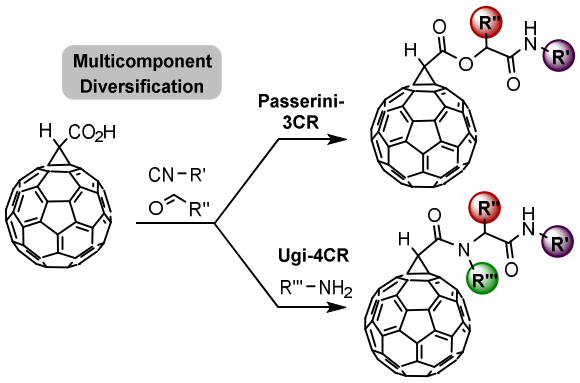
Summary and Outlook

Fullerenes are a unique class of compounds with peculiar and intrinsic properties that up to this day still surprises and interest many research fields. The exo-functionalization of its cage-like structure has been the favoured protocol to obtain new derivatives, employing the many available methods in the literature, which later can be used in different applications, e.g., photodynamic therapy. Isocyande-based multicomponent reactions (IMCRs) are highly versatile and successful procedures, adding three or more diversity points in a single step, and so far, have not been applied in combination with fullerenes. Knowing the great advantages of the use of IMCR for the generation of large molecular libraries, the goal of this PhD thesis was to incorporate IMCR in the construction of novel fullerene derivatives, creating new and appealing scaffolds that can be added to the fullerene derivatives toolbox.

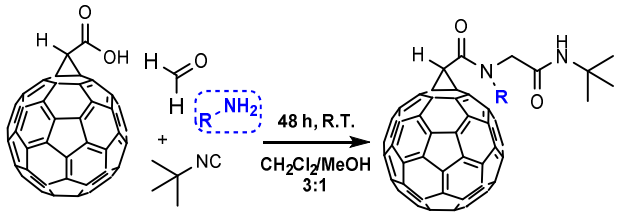
Chapter 1 underlines the main aspects of fullerenes (properties, reactions and applications), photodynamic therapy and the Passerini and Ugi multicomponent reactions.

In **Chapter 2**, we develop a methodology to decorate fullerenes bearing a carboxylic acid *via* the Ugi and Passerini reaction. With this protocol twelve new fullereno-Ugi products and twelve new fullereno-Passerini products were synthesized. Representative compounds were evaluated as photosensitizers for their use in photodynamic therapy, awarding good results (Scheme 1).



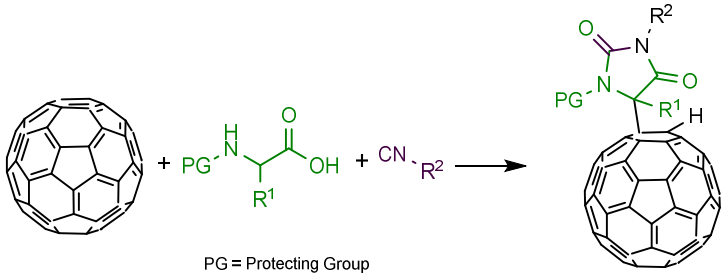
Scheme 1. Multicomponent diversification of C_{60} by Passerini and Ugi reactions.

The scope expansion of the method developed above is presented in **Chapter 3**, where different amino components were screened for the Ugi reaction, producing fifteen new fullereno-Ugi derivatives. Complementary follow up reactions were performed in order to increase the complexity of the achieved products, yielding four additional products by means of click and coupling reactions (Scheme 2).



Scheme 2. Scope expansion for the Ugi four-component reaction.

Finally, **Chapter 4** highlights a new multicomponent process involving fullerene C_{60}, *N*-protected amino acids, and isocyanides, giving rise to an unusual product structure (Scheme 3).



Scheme 3. IMCR with fullerene C_{60}, *N*-protected amino acids and isocyanides.

Zusammenfassung und Ausblick

Fullerene sind eine einzigartige Verbindungsklasse mit charakteristischen und intrinsischen Eigenschaften, die bis heute unerwartete und interessante Ergebnisse in breit gefächerten Forschungsgebieten finden. Die Exo-Funktionalisierung von käfigartigen Strukturen dient bislang als bevorzugte Methode, um neue Fullerenderivate zu synthetisieren. Durch die Literatur sind verschiedene methodische Vorgehen bekannt, die in unterschiedlichen Gebieten angewendet werden können, wie beispielsweise bei der photodynamischen Therapie. Isocyanid-basierende Multikomponentenreaktionen (IMCR) werden als vielseitige und erfolgreich implementierte Prozeduren verwendet, bei denen drei oder mehr Reaktionspartner in einem Syntheseschritt das gewünschte Produkt bilden. Derzeit ist keine IMCR-Anwendung auf dem Forschungsgebiet der Fullerene bekannt. Durch deren vorteilhafte Verwendung um große molekulare Bibliotheken zu erstellen, soll das Ziel dieser Doktorarbeit darin bestehen, neue Fullerenderivate mit Hilfe von IMCR zu generieren.

Kapitel 1 hebt die zentralen Aspekte von Fulleren, der photodynamischen Therapie und der Passerini und Ugi Multikomponentenreaktion hervor.

Kapitel 2 befasst sich mit der methodischen Entwicklung von carboxylierten Fullerenen mittels Ugi und Passerini Reaktionen. Mit Hilfe dieses Protokolls konnten zwölf neue fullereno-Ugiprodukte und zwölf neue fullereno-Passeriniprodukte synthetisiert werden (Abbildung 1). Gute Ergbenisse konnten unter der Verwendung dieser Verbindungen als Photosensibilisatoren in der photodynamischen Therapie erzielt werden.

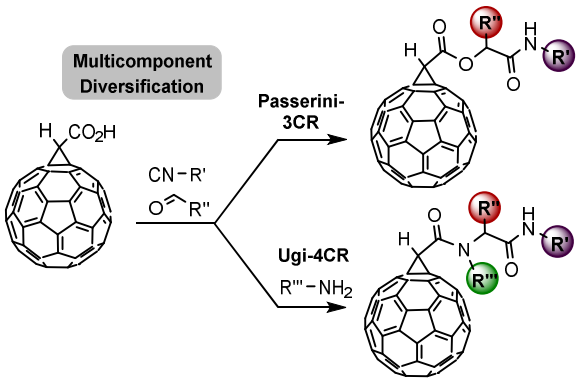


Abbildung 1. Multikomponenten diversifizierung von C_{60} mittels Passerini und Ugi Reaktion.

Die zuvor entwickelte Methode wird in **Kapitel 3** verwendet, um das Substratspektrum zu erweitern. Unter Verwendung von verschiedenen Aminkomponenten in der Ugireaktion konnten fünfzehn neue fullereno-Ugiderivate synthetisiert wurden (Abbildung 2). Um die Komplexität der synthetisierten Produkte zu bewerkstelligen, wurden Folgereaktionen durchgeführt. Die resultierenden vier Produkte konnten durch Klick- und Kupplungsreaktionen erzeugt werden.

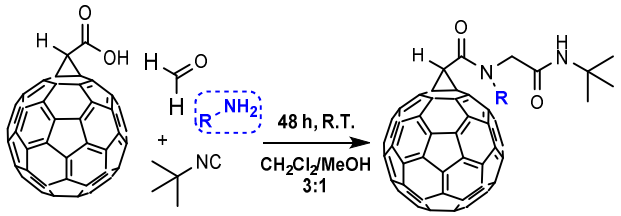


Abbildung 2. Erweiterung des Substratspektrums für die Ugi-4CR.

Kapitel 4 befasst sich mit der Entwicklung einer Multikompentenreaktion um strukturell-neuartige Produkte unter Verwendung von C_{60} Fullerenen, *N*-geschützten Aminosäuren und Isocyaniden zu kreieren (Abbildung 3).

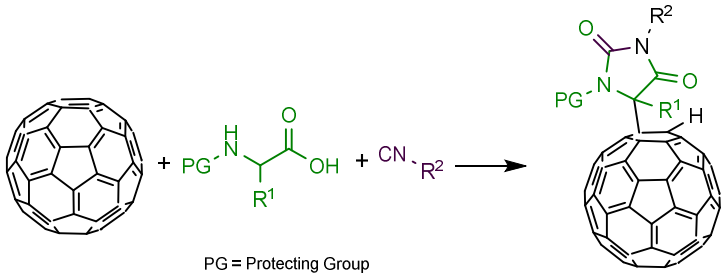


Abbildung 3. IMCR mit C_{60} Fullerenen, *N*-geschützten Aminosäuren und Isocyaniden.

Attachments

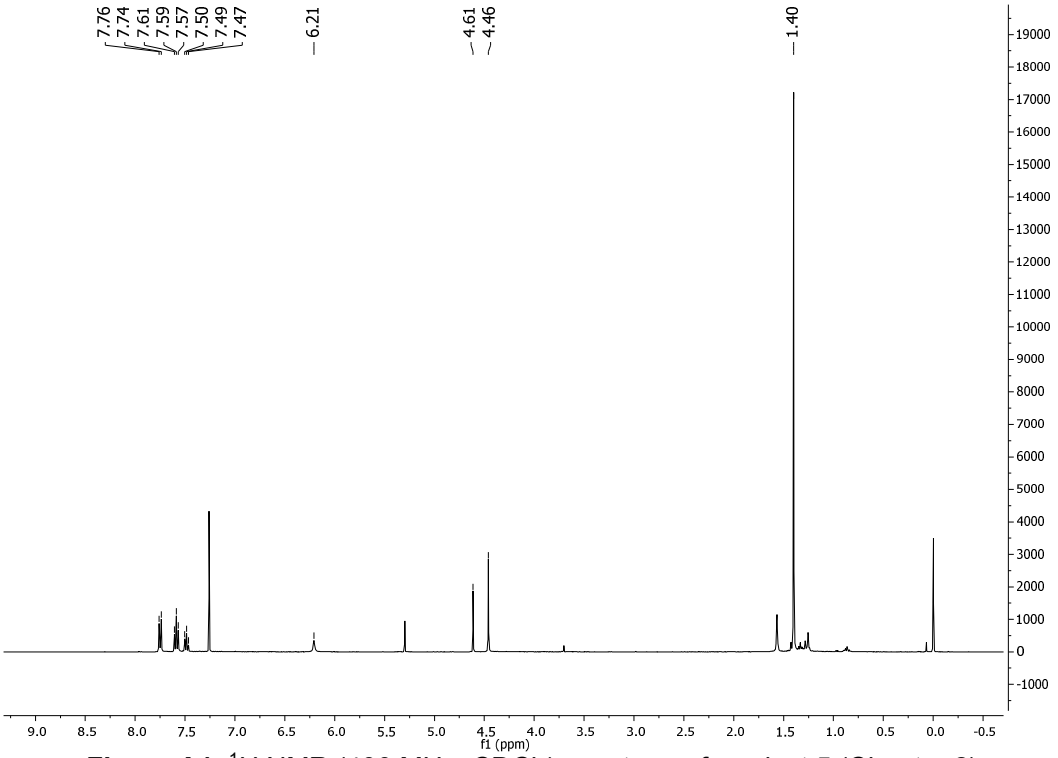


Figure A1. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of product **5** (Chapter 2).

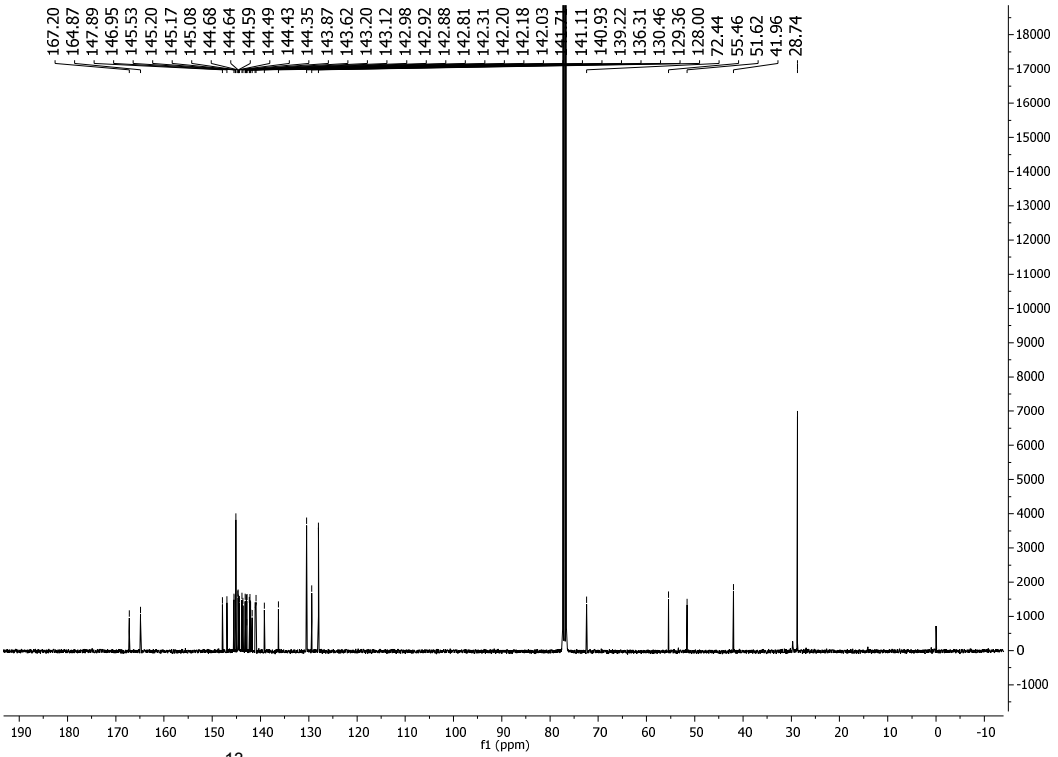


Figure A2. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of product **5** (Chapter 2).

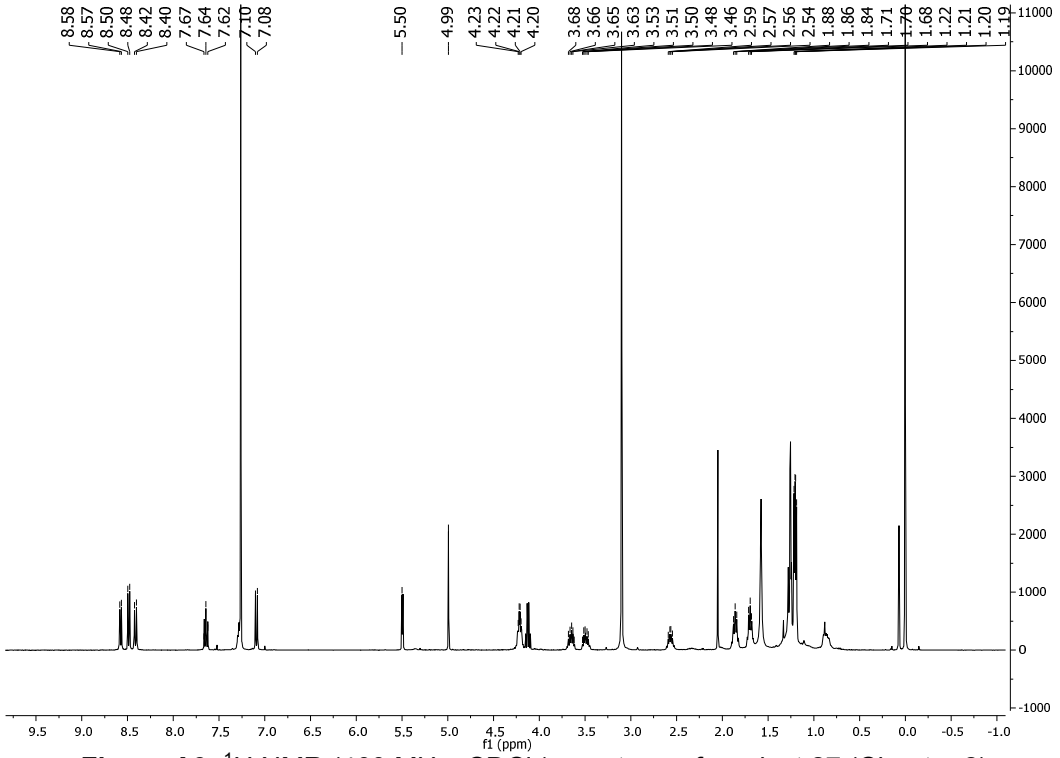


Figure A3. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of product **27** (Chapter 2).

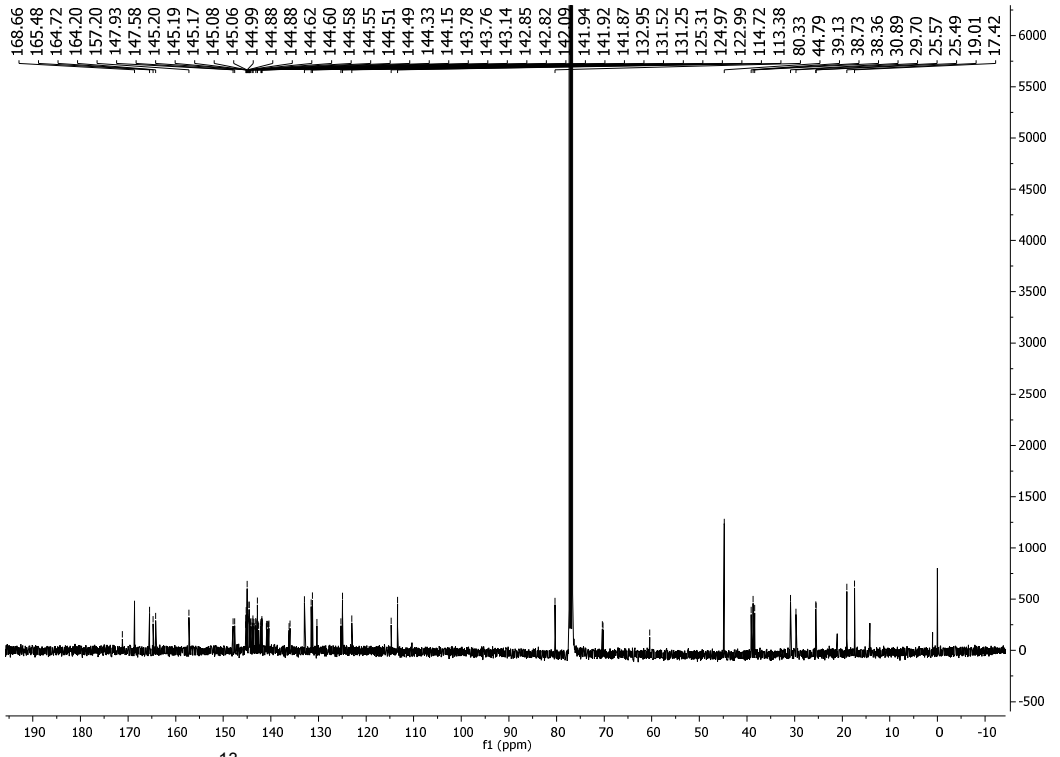


Figure A4. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of product **27** (Chapter 2).

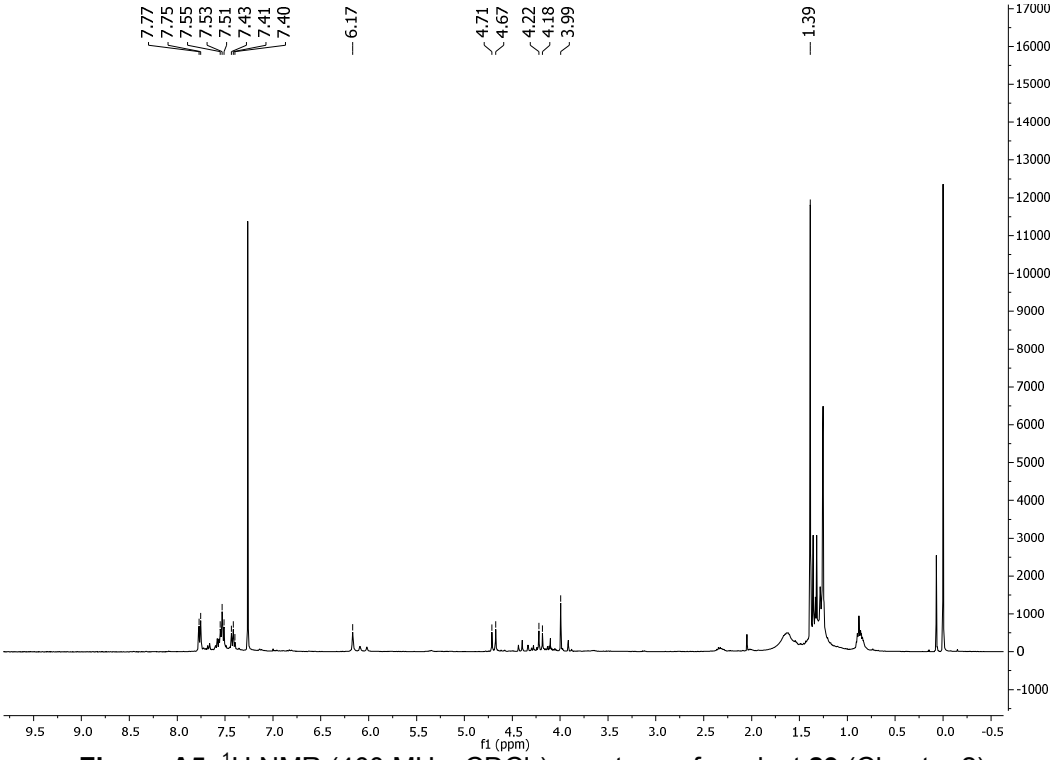


Figure A5. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of product **29** (Chapter 2).

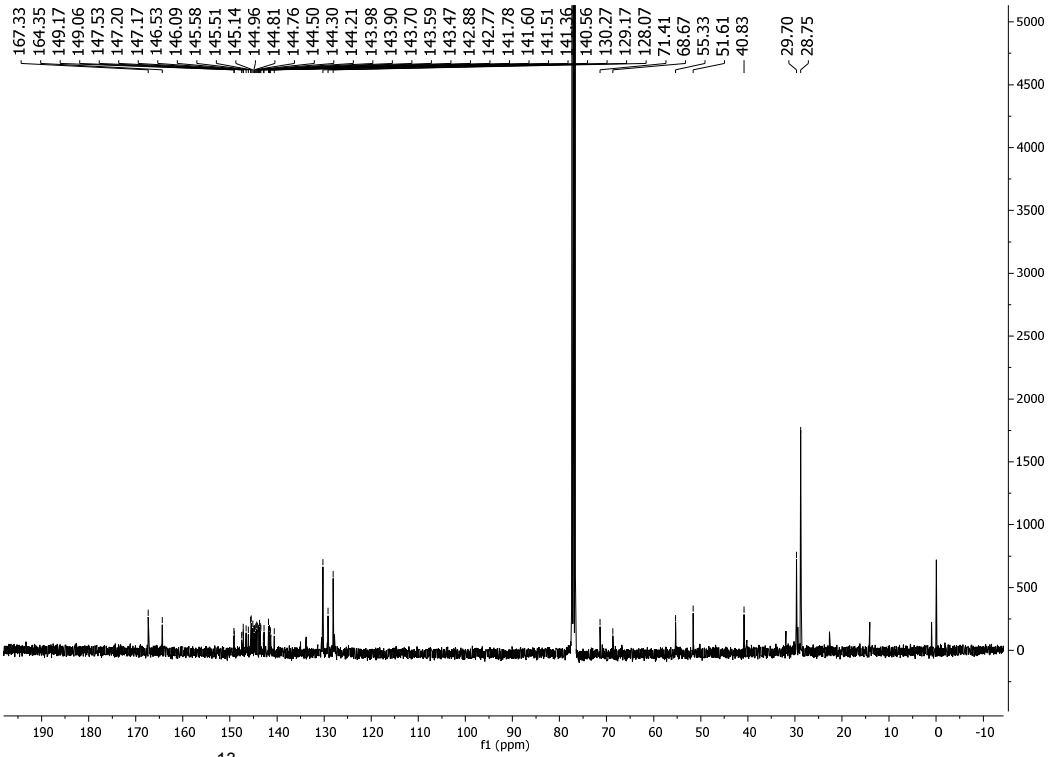


Figure A6. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of product **29** (Chapter 2).

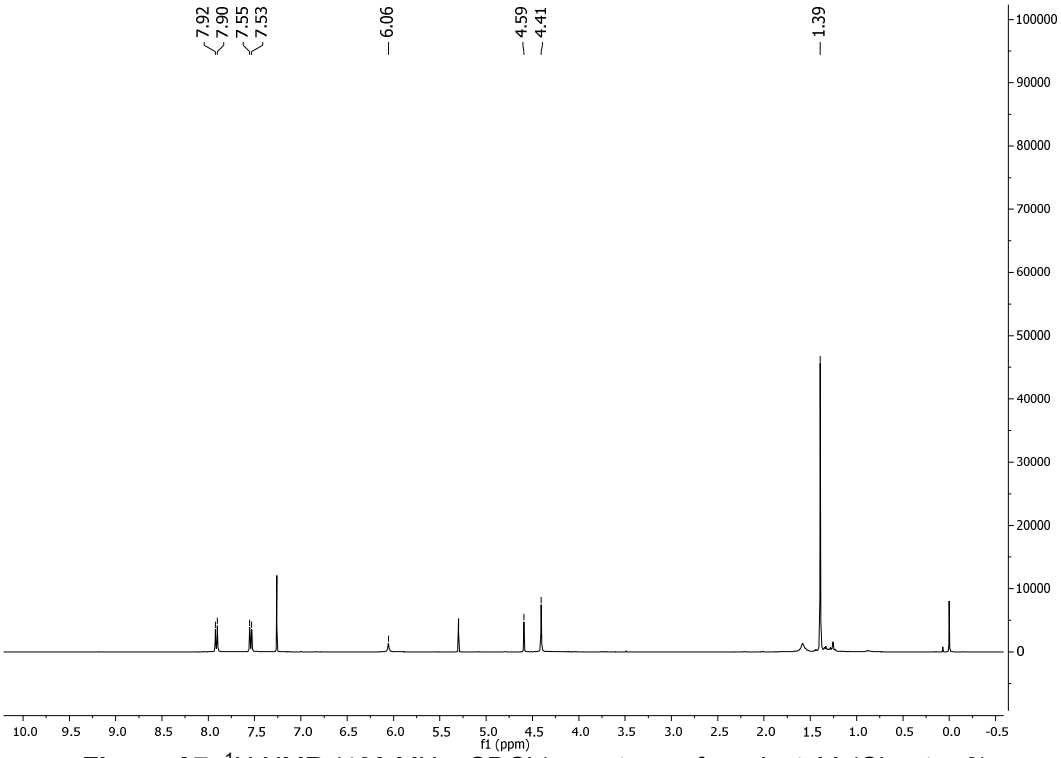


Figure A7. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of product **11** (Chapter 3).

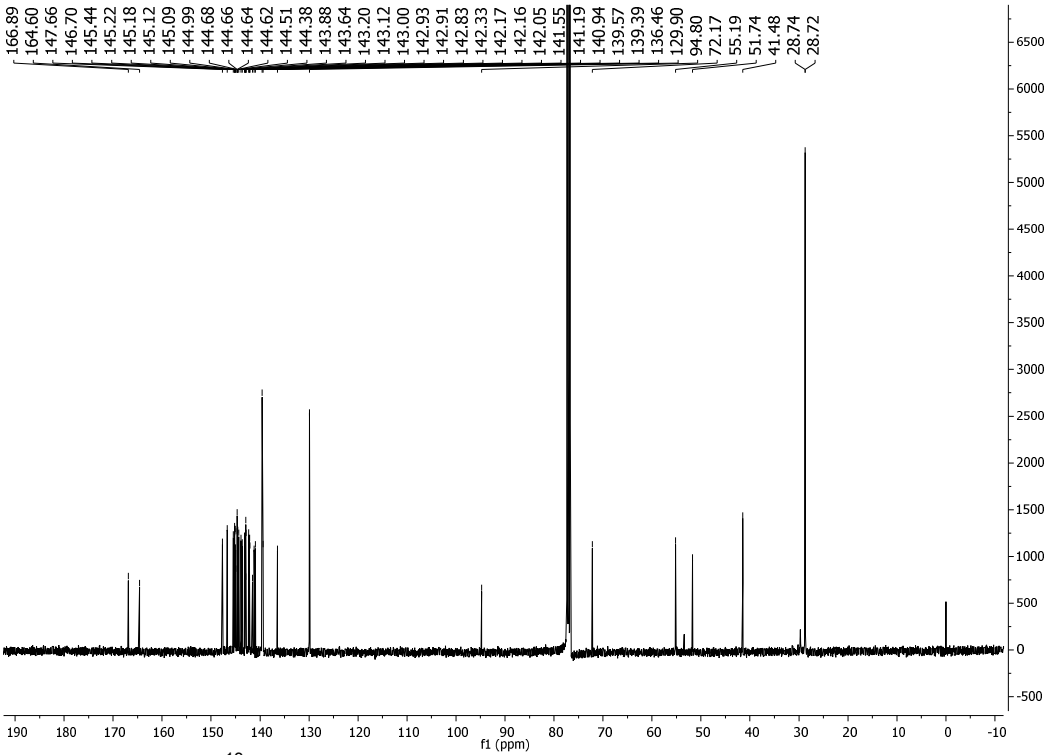


Figure A8. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of product **11** (Chapter 3).

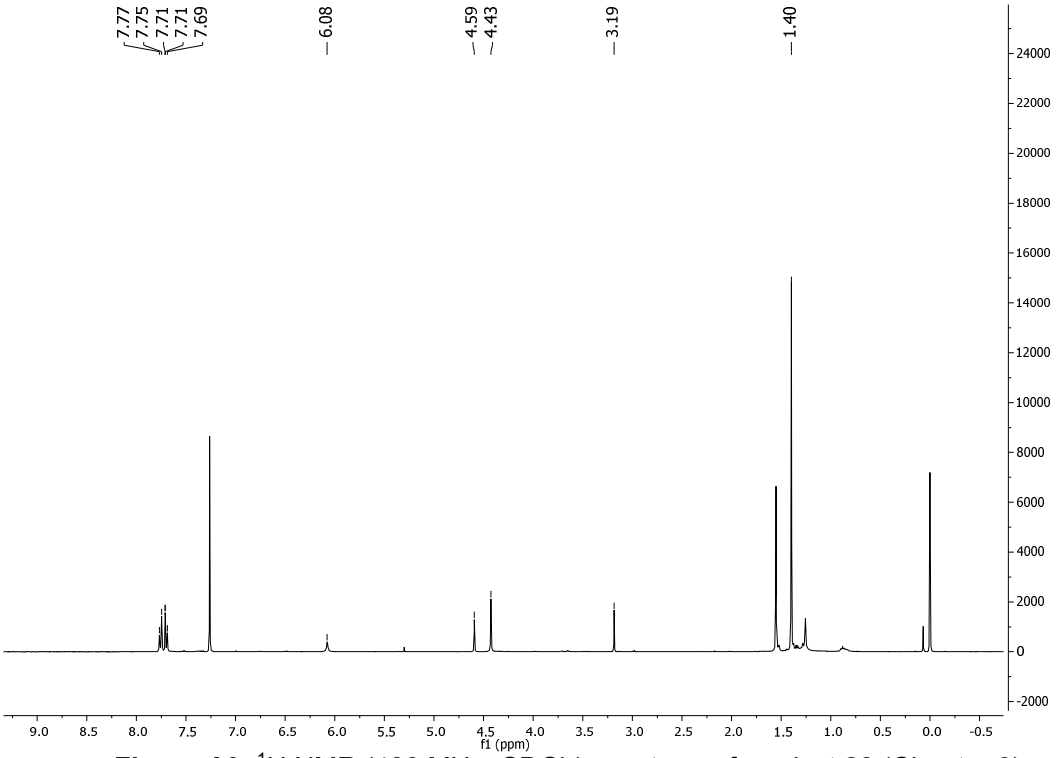


Figure A9. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of product **20** (Chapter 3).

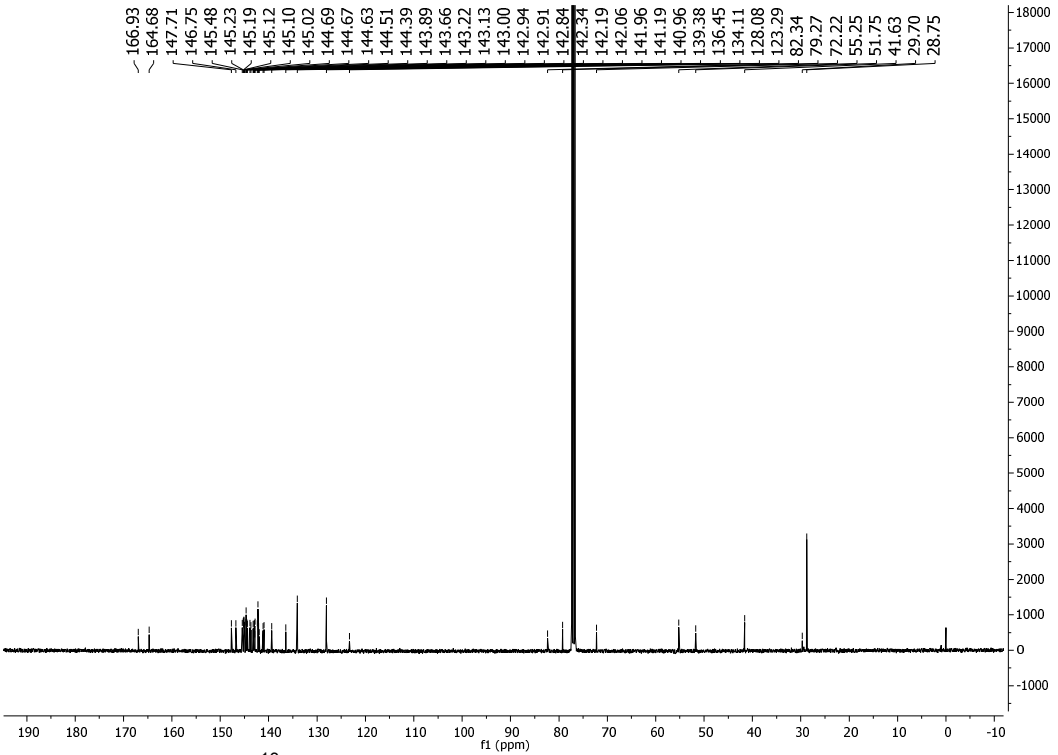


Figure A10. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of product **20** (Chapter 3).

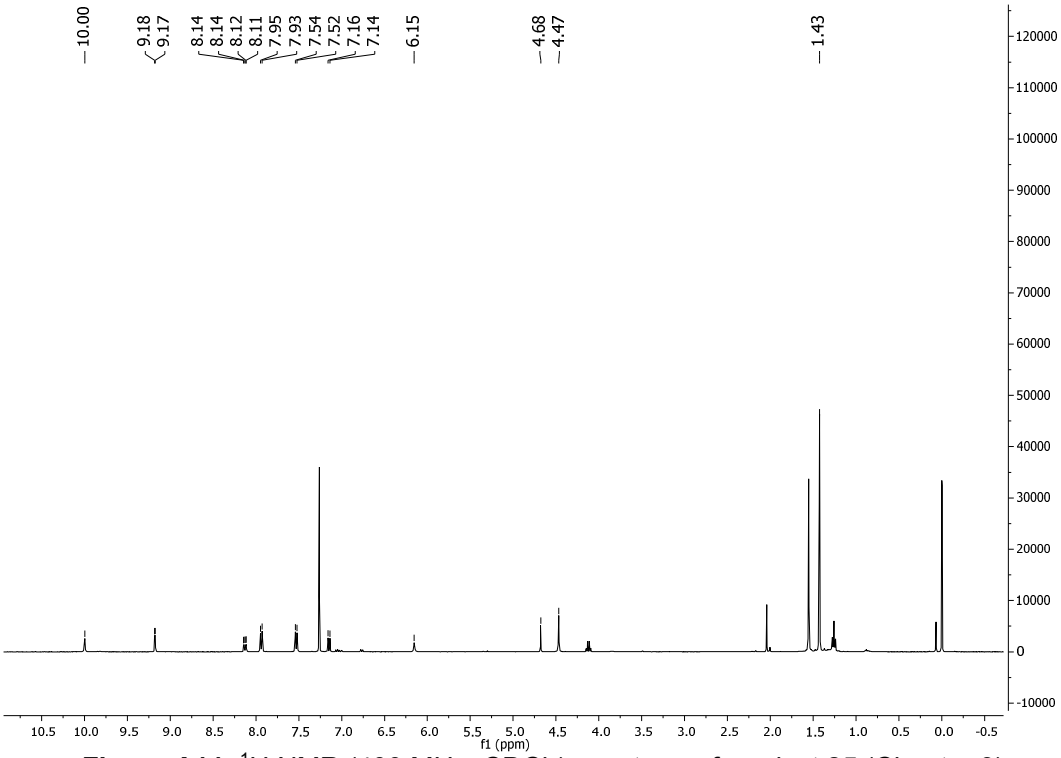


Figure A11. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of product **25** (Chapter 3).

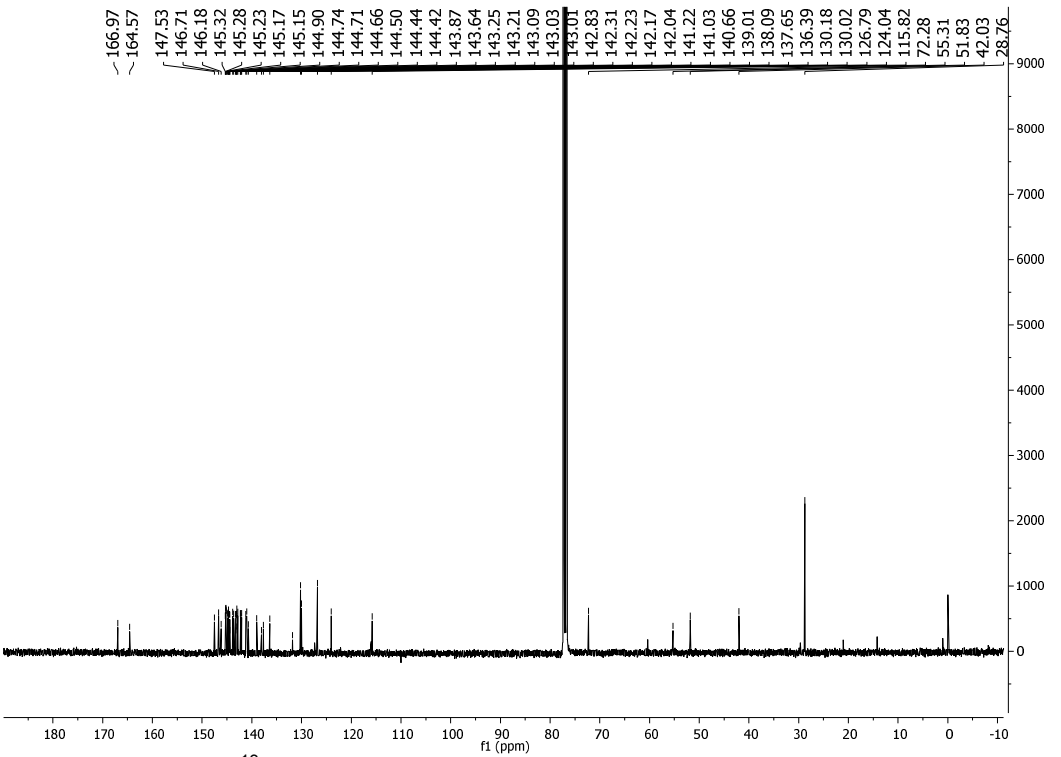


Figure A12. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of product **25** (Chapter 3).

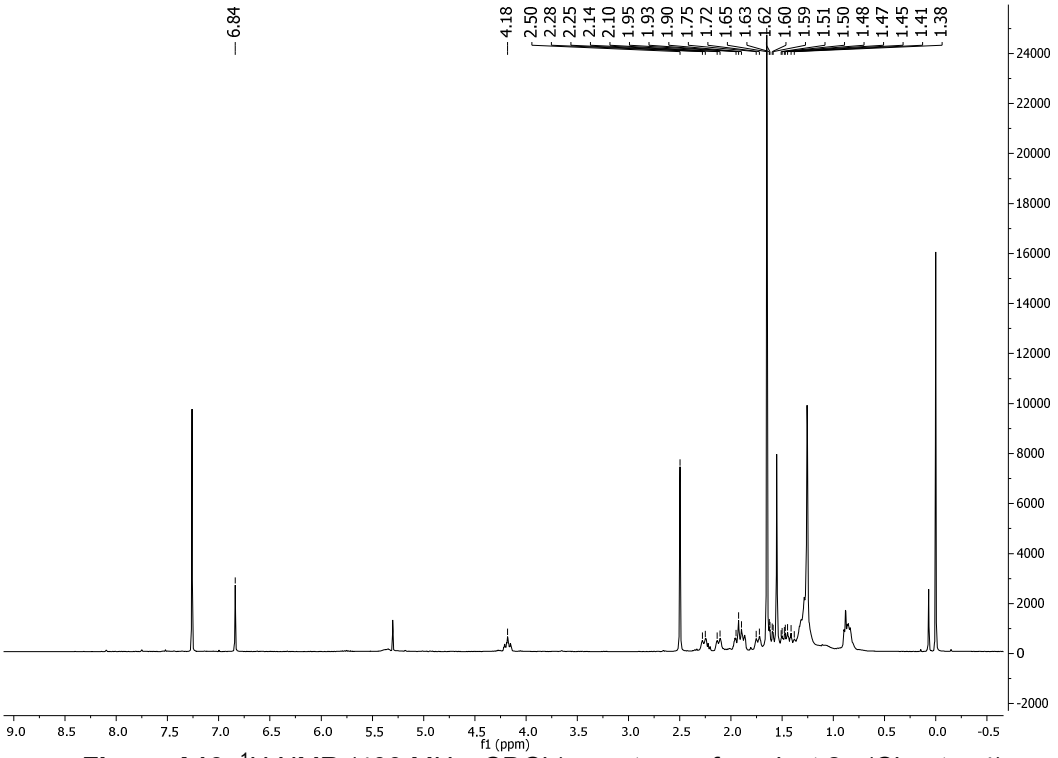


Figure A13. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of product **2a** (Chapter 4).

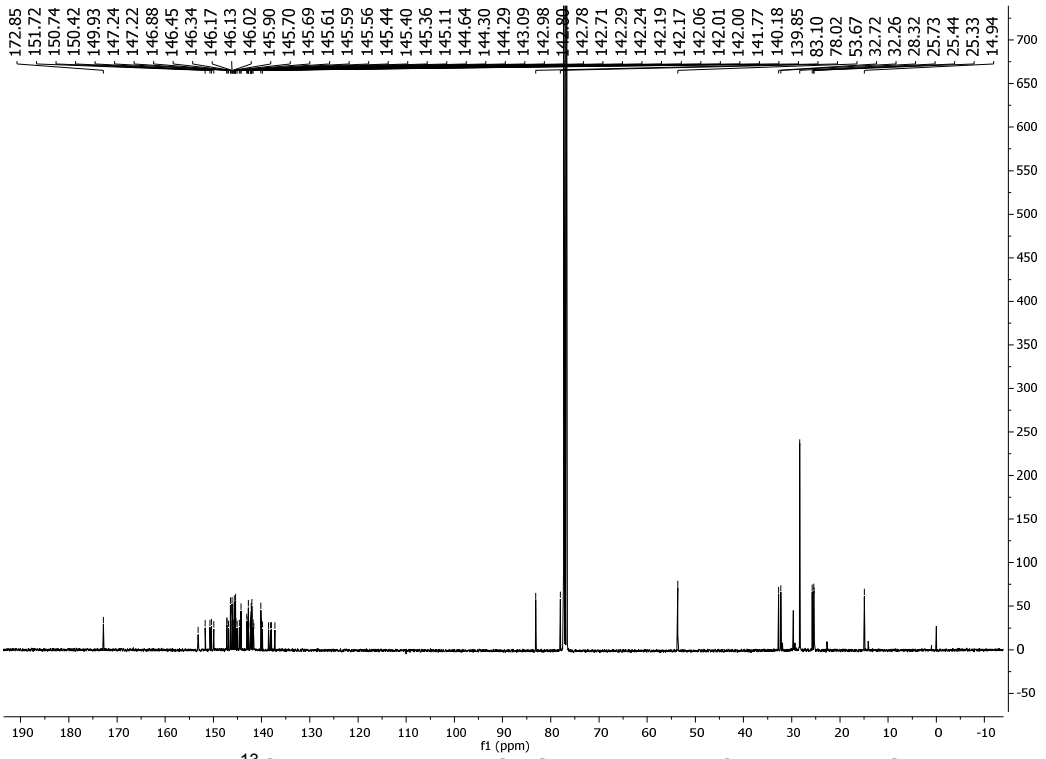


Figure A14. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of product **2a** (Chapter 4).

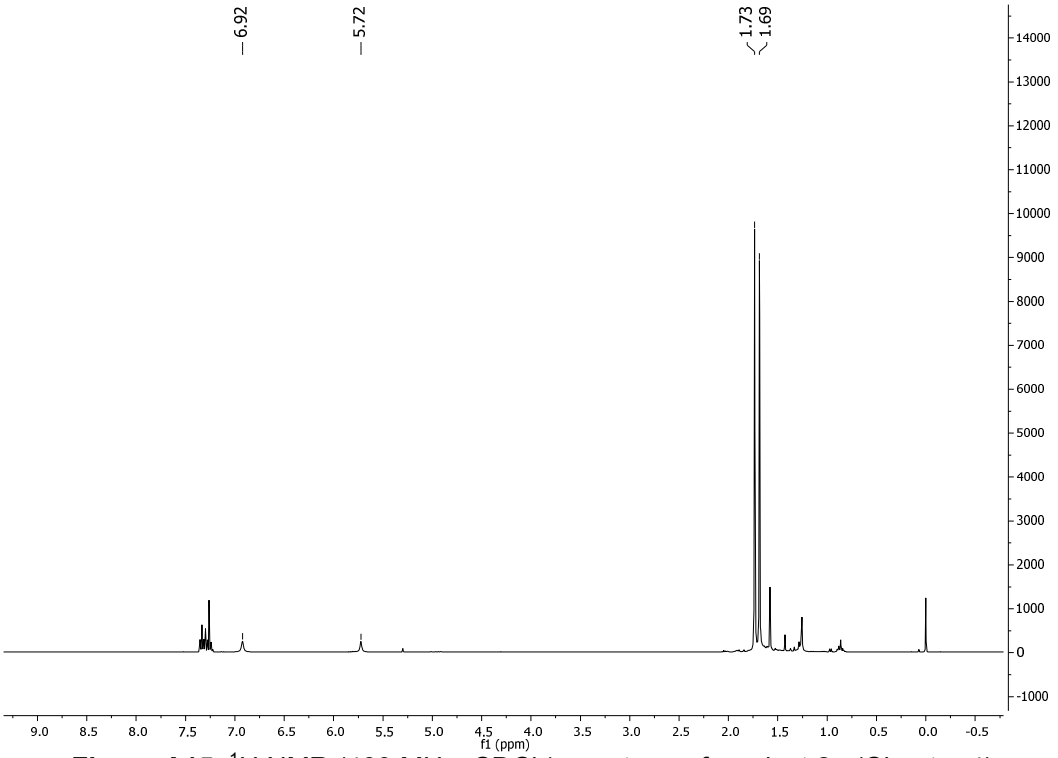


Figure A15. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of product **2e** (Chapter 4).

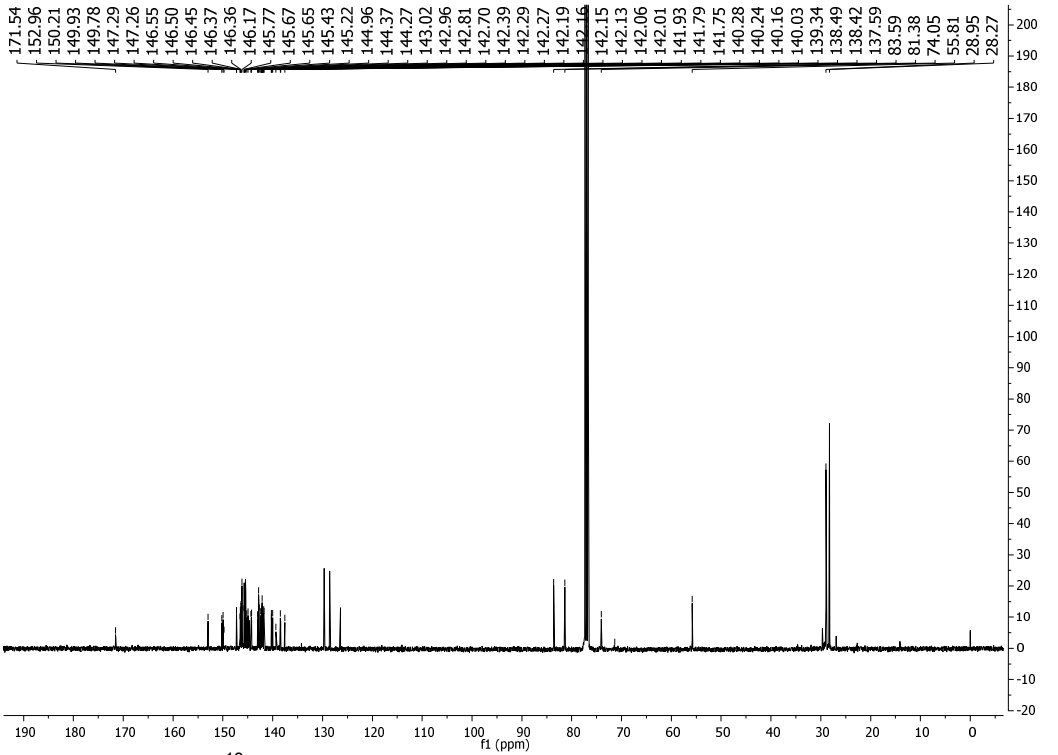


Figure A16. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of product **2e** (Chapter 4).

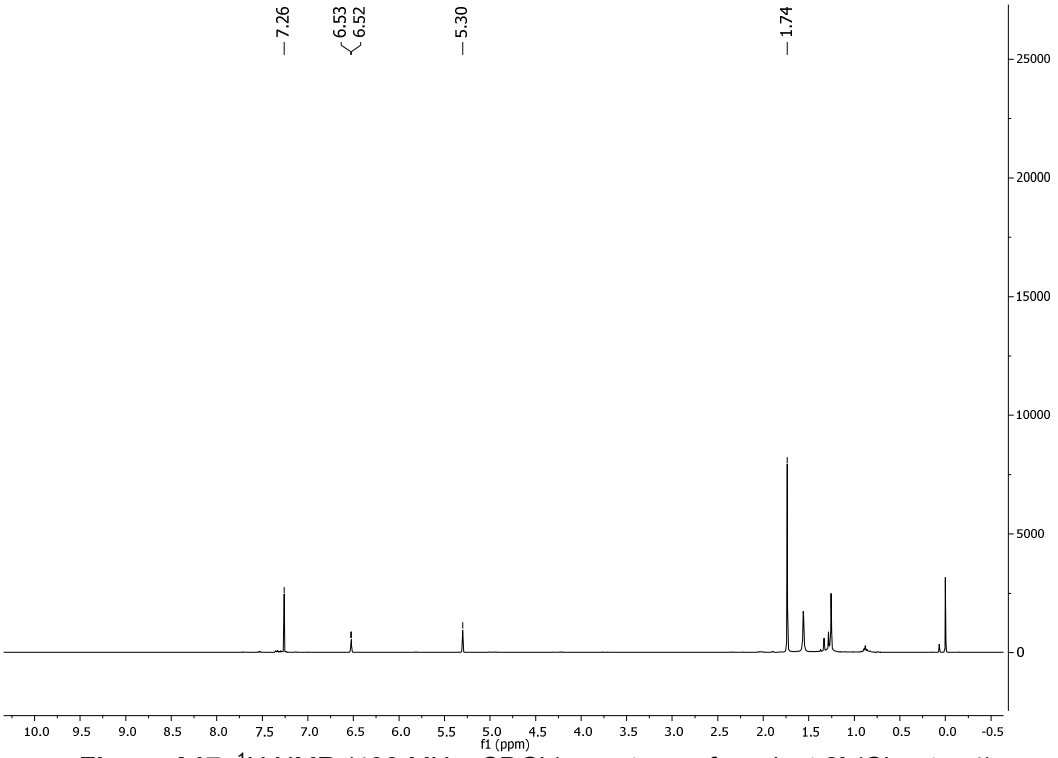


Figure A17. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of product **2j** (Chapter 4).

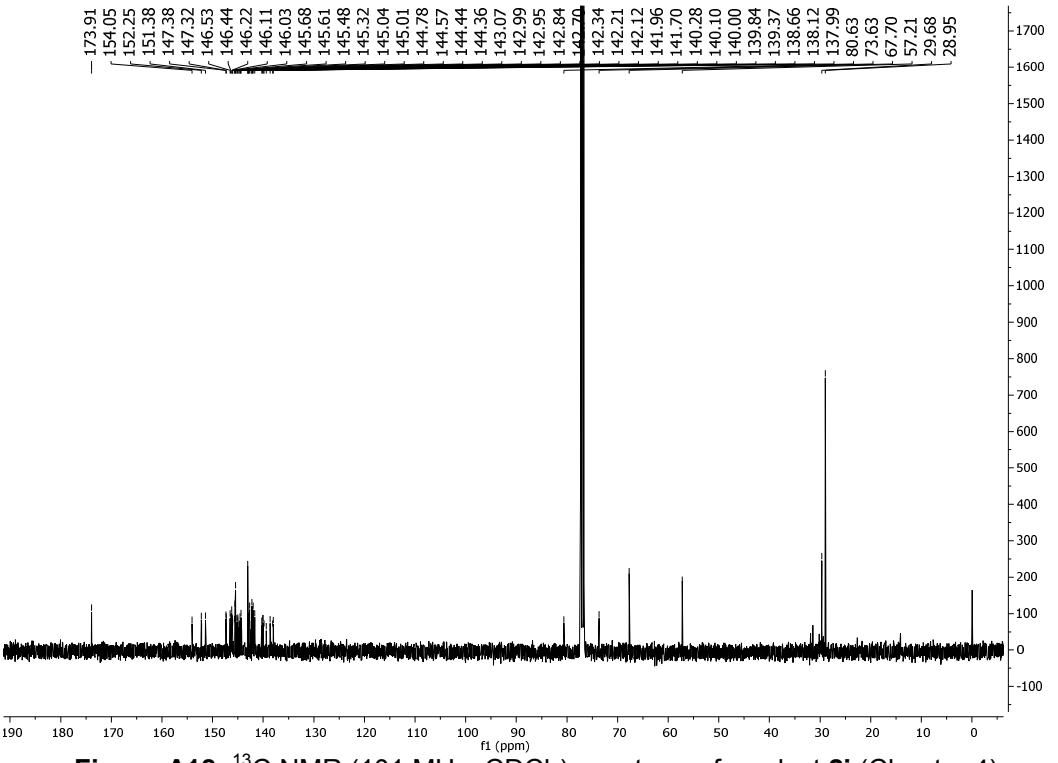


Figure A18. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of product **2j** (Chapter 4).

Institute internal substance assignments

Chapter 2

Product number	Three letter code BRB	Product number	Three letter code BRB
1a	111	**17**	207
1b	112	**18**	219
3	110	**19**	209
4	216	**20**	223
5	217	**21**	346
6	204	**22**	345
7	228	**23**	224
8	239	**24**	320
9	226	**25**	304
10	230	**26**	293
11	231	**27**	336
12	356	**28a**	276
13	321	**28b**	291
14	323	**29**	324
15	353	**30**	326
16	208		

Chapter 3

Product number	Three letter code BRB	Product number	Three letter code BRB
1a	111	**19**	524
1b	112	**20**	375
3	110	**21**	374
4	401	**22**	512
5	387	**23**	518
6	385	**24**	500
7	388	**25**	519
8	217	**26**	354
9	228	**27**	412
10	229	**28**	355
11	495	**29**	521
12	351	**30**	522
13	517	**31**	523
14	511	**32**	461
15	520	**33**	446
16	516	**34**	447
17	376	**35**	448
18	515	**36**	504

Chapter 4

Product number	Three letter code BRB	Product number	Three letter code BRB
2a	118	**2f**	145
2b	123	**2g**	527
2c	128	**2h**	134
2d	126	**2i**	135
2e	133	**2j**	141

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3. Languages

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4. Professional Experience

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2007-2008 Institutional contract with Câmara Municipal de Santa Maria - CMSM. Parliamentary Assistant, 20 hours weekly.

5. Selected Conferences

2017 Ravanello, B. B.; Rodrigues, O. E. D.; Villetti, M. A.; Westermann, B. Peptoid-modified fullerenes and their applications. At 18th international conference on the science and application of nanotubes and low-dimensional materials, Belo Horizonte, Brazil. Poster presentation.

6. Bibliographic Production

2012

Vargas, J.; Narayanaperumal, S.; Gul, K.; Ravanello, B. B.; Soares, L. C.; Alves, Camilla F. S.; Schneider, T.; Vaucher, R. A.; Santos, Roberto C.V.; Rodrigues, O. E. D. *Tetrahedron* **2012**, 68, 10444-10448.

2018

Ravanello, B. B.; Seixas, N.; Rodrigues, O. E. D.; da Silva, R. S.; Villetti, M. A.; Frolov, A.; Rivera, D. G.; Westermann, B.; *Chem. Eur. J.* **2018**, 24, 9788-9793.