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Supramolecular masks for the regioselective synthesis of Diels–Alder hetero-tris-adduct C_{60} fullerene

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Herein, we report the regioselective hetero-tris-functionalization of fullerenes *via* a sequential Diels–Alder cycloaddition strategy. The first addend is introduced onto C_{60} through a cascade process involving a Ru-catalyzed cycloisomerization of 1,6-enynes, followed by a Diels–Alder reaction with C_{60}. Subsequently, supramolecular nanocapsules are employed as regioselective masks, enabling enhanced control over the formation of a hetero-tris-adduct bearing two pentacene units. These units are positioned equatorially with respect to the initial addend and adopt a *trans*-1 relative orientation. Notably, a single pure tris-regioisomer, *e*,*e*,*t*1(*l*), is obtained for both **2a-Pn$_2$** and **2d-Pn$_2$**. Access to pure-isomer hetero-tris Diels–Alder adducts is unprecedented and highlights the broad potential of the supramolecular mask strategy.

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Introduction

Interest in C_{60} has grown considerably since the first large-scale production of this compound thirty-five years ago.[1] In order to enhance the utility and broaden the applications of fullerenes, they need to be functionalized.[2] Structural modifications by introducing specific functional groups serve multiple purposes, including enhancing solubility in organic solvents, which is crucial for solution-based processing in materials science, and improving solubility in water, a key factor for biomedical applications.[3] Moreover, by introducing specific functional groups, the electronic properties of the fullerene cage can be fine-tuned, thereby improving photovoltaic performance in organic and perovskite solar cells.[4]

Nowadays, highly efficient synthetic methods are available to introduce a single addend into pristine C_{60}. The Diels–Alder (DA) cycloaddition reaction, in particular, has been widely used to synthesize a large number of fullerene derivatives in which the fullerene molecule behaves as a dienophile due to the electron-deficient nature of its [6,6] bonds.[5] The Diels–Alder cycloaddition can proceed either with a preformed diene or *via in situ* generation of the diene from unsaturated substrates through a transition metal-catalysed cycloisomerization.[6] This latter strategy allows for the diversification of both functional groups and scaffolds that can be attached to the fullerene.

However, once the first addend is attached to the fullerene cage, 9 different [6,6] bonds remain available for a second addition and, considering a threefold addition, the number of theoretically possible regioisomers increases from 9 to 46. This growing complexity makes it increasingly difficult to isolate pure isomers, complicating their practical applications in the targeted fields. Moreover, isolating these regioisomeric mixtures typically requires multistep high-performance liquid chromatography, which is a costly, labour-intensive, and time-consuming process that often proves impractical. Therefore, since properties of the resulting adducts are largely determined by the addition site on the fullerene cage, new approaches are needed to achieve controlled poly-functionalization of fullerenes, enhancing itero-, chemo-, regio-, and stereoselectivity to limit the formation of unwanted isomers.

Among these multiple addition products, tris-adducts are of special interest. In the area of solar energy conversion, they often exhibit higher LUMO energy levels than their mono- or bis-substituted counterparts, which can enhance performance in organic solar cells.[7] Additionally, the *e*,*e*,*e* trismalonic acid fullerene derivative[8] exhibits pronounced water solubility, enhancing its suitability for biomedical applications, particularly as an antioxidant agent with potential use in treating degenerative diseases.[9] In material science, the presence of three functional sites can also afford the construction of

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complex architectures, including dendrimers[10] and polymers. In a particular case, a self-assembly ultrathin film made from a C_{60} triscarboxylate ion and diazoresin showed good load-bearing and lubricating properties.[11]

The first powerful methodology for the regioselective synthesis of selected tris-adducts of C_{60} was the tether-directed remote functionalization approach[12] pioneered by Diederich *et al.*[13] Given the limited number of methods available for accessing tris-functionalized adducts, this strategy marked a breakthrough. The use of tethered addend systems, whether with permanent or temporary tethers, has enabled relatively easy access to otherwise highly disfavoured addition patterns. One option is through the introduction of a temporary tether that blocks certain positions and directs the tris-functionalization, especially the Bingel reaction, towards specific positions on the fullerene.[14] Another option is the use of tripodal tethers, which, depending on their length and rigidity, directly guide the tris-functionalization to occur at only three defined bonds on the fullerene.[15]

An alternative, promising strategy is based on the use of supramolecular receptors as functionalization platforms for fullerenes. Our pioneering Supramolecular Mask Strategy (SMS),[16] *i.e.* using encapsulated fullerenes in supramolecular nanocapsules, targets the synthesis of isomer-pure poly-functionalized fullerenes, and consists of a regioselective fullerene functionalization technique in which a host molecule, exhibiting a high affinity for the fullerene guest, shields part of the fullerene surface, unveiling the sites exposed and available for chemical modification (Fig. 1a). The SMS was initially applied to C_{60} in combination with the Bingel reaction, affording the pure *e*,*e*,*e*,*e* tetrakis-Et_4-C_{60} adduct.[16a] Furthermore, the SMS was expanded for the Diels–Alder reaction, leading to the selective formation of the *e*,*e* bis-An_2-C_{60}.[16b] Upon increasing the acene to pentacene, the *trans*-1 bis-Pn_2-C_{60} was obtained. These DA-adducts were subsequently subjected to the SMS under Bingel conditions to access hetero-tris-adducts through the combination of two distinct reactions. We hypothesised that Diels–Alder cycloaddends could be used as a handle to obtain tris-adducts of C_{60} as regioisomerically pure adducts under the SMS. Hence, we describe in this work the regioselective hetero-tris-functionalization of fullerene using Diels–Alder cycloadditions in a sequential strategy. A first addend is introduced onto the fullerene through a cascade process involving a Ru-catalyzed cycloisomerization of 1,6-enynes followed by a Diels–Alder reaction with C_{60}. Subsequently, nanocapsules are employed as supramolecular masks to obtain high levels of regioselectivity towards a hetero-tris-adduct containing two pentacene units positioned equatorially with respect to the initial addend and adopting a *trans*-1 relative orientation (Fig. 1b). The access to pure-isomer hetero-tris-DA-adducts is unprecedented and shows the broad potential of the supramolecular mask strategy.

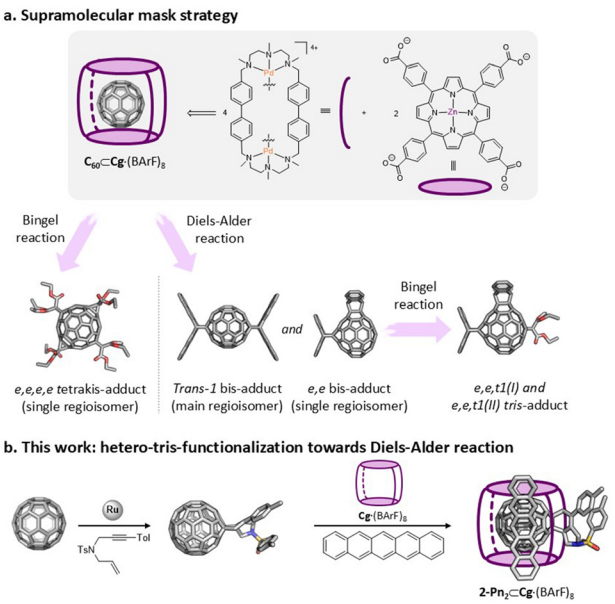

Fig. 1 (a) Schematic representation of the synthesis of the reported tetragonal prismatic **Cg**·$(BArF)_8$ cage and its application in the functionalization of C_{60}, obtaining pure regio-isomers. (b) Schematic representation of this work: hetero-tris-functionalization of C_{60} by Diels–Alder cycloadditions in a sequential strategy.

Results and discussion

Synthesis and encapsulation of the mono-adducts 2

We have worked extensively on the development of cascade processes to obtain monofunctionalized fullerene and fulleroid derivatives.[6f,g,h,i] In this context, we turned our attention to the preparation of a series of non-symmetric mono-cycloadducts **2a–2e** by a cascade process encompassing a Ru-catalyzed cycloisomerization of 1,6-enynes **1a–1e** followed by a Diels–Alder reaction with C_{60}. Although the Ru-catalyzed cycloisomerization of 1,6-enynes is well established and known to afford 1,3-dienes,[17] it has never been applied to generate a diene, either *in situ* or in isolated form, that subsequently reacts with C_{60}. With this unexplored reactivity as a target, we selected the cascade reaction between NTs-tethered enyne **1a** and pristine fullerene under ruthenium catalysis as a model system for optimization (see Table S1). The best reaction conditions were found to be 2.2 equivalents of the 1,6-enyne **1**, 1 equivalent of C_{60}, using a 10 mol% of Grubbs 1st generation catalyst in *o*-DCB at 90 °C.

The scope of the process is shown in Scheme 1. The reaction displayed a broad substrate scope and proceeded efficiently with both aryl/heteroaryl and alkyl substituents on the alkyne terminus of the enyne. Electron-donating groups in the phenyl ring gave good yields (**2a**, 53% yield), whereas strong electron-withdrawing substituents reduced the efficiency (**2b**, 24% yield). Notably, thiophenyl (**2c**, 52% yield) and alkyl alkynes (**2d**, 64% yield) were well tolerated, providing good yields, and modification of the tether (tosyl *vs.* *tert*-butyl malonate) maintained the reactivity, affording a 36% yield of the corresponding product **2e**.

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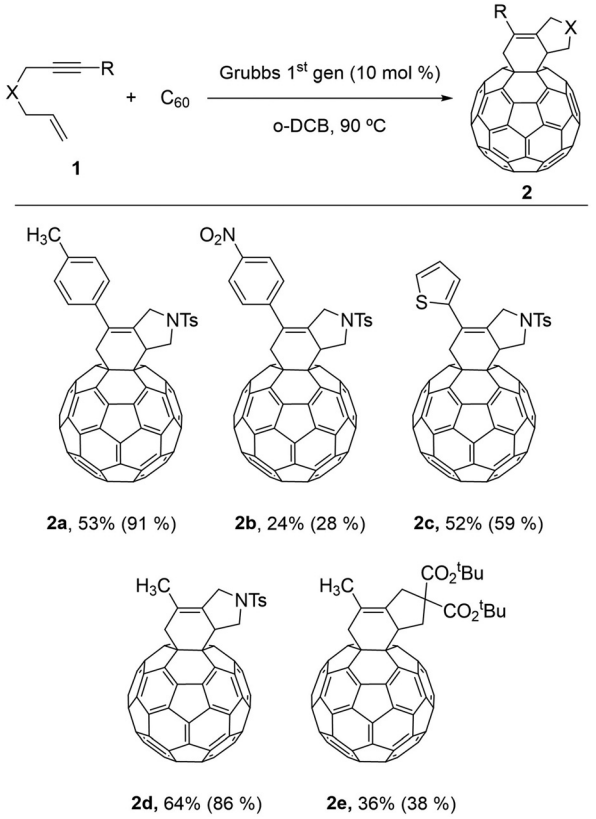

Scheme 1 Synthesis of compounds **2a–2e** by cycloaddition of enynes **1** with C_{60}. The values in parentheses are the yields based on the amount of C_{60} consumed.

Based on their structural differences, three of the mono-derivatives **2a**, **2d** and **2e** were selected to attempt the SMS-based Diels–Alder functionalization with pentacene. First, the host–guest complexes were prepared by adding two equivalents of a toluene solution of the mono-derivative **2** to an acetonitrile solution of the **Cg**·$(BArF)_8$ cage, maintaining a solvent ratio of 4 : 1 toluene : acetonitrile. After 24 hours of reaction, the HRMS analysis confirmed the quantitative formation of the host–guest complex (Fig. S23–S25).

Diels–Alder reaction with pentacene on the 2a mono-adduct

We first focused on the regiofunctionalization of **2a** with pentacene. The reaction was carried out under the following conditions: 65 °C, 24 h, cage concentration of 10^{-3} M, acetonitrile (MeCN) : dichloromethane (DCM) (3 : 1) solvent mixture, and under N_2 atmosphere in the dark (Fig. 2a). Upon addition of 1.5 equivalents of pentacene, the reaction evolved towards the formation of a mixture of bis- and tris-adducts. Increasing the amount of pentacene up to 2.2 equivalents likewise led mainly to tris-adduct formation, albeit with low amounts of bis-adducts detected by HRMS (Fig. 2b and S26).

Upon completion of the reaction, the release of the functionalized fullerenes from the nanocapsule was then investigated. Initially, a solvent-washing protocol was attempted, which was expected to leave the empty cage in the solid state, fully releasing the encapsulated fullerenes into solution; this involved suspending the host–guest complex in CS_2, followed by sonication. Under these conditions, the cage indeed remained in the solid, and fullerene release was observed. However, HRMS analysis of the recovered cage still revealed a major peak corresponding to the encapsulated tris-adduct. Consequently, an acid-mediated strategy was selected to disassemble the nanocapsule and ensure the complete liberation of the guest. Hence, trifluoromethanesulfonic acid was added to the acetonitrile solution of the cage, after which the fullerenes were recovered by extractions with toluene.

After the release of the functionalized fullerenes, the reaction crude was initially analysed by HPLC. The resulting chromatogram displayed a predominant peak (Fig. 2c and S27; R_t = 9.70 min) together with several minor peaks, indicative of the formation of multiple regioisomers. To unravel the nature of the main peak, the crude mixture was purified by preparative thin-layer chromatography using toluene as eluent. The isolated product was subsequently reinjected into the HPLC, confirming its correspondence to the major peak through an identical absorption profile (Fig. 2e). The isolated yield was determined to be 56.7% by HPLC analysis, using the C_{60} as an internal standard.

The HRMS analysis confirmed that the C_{60} derivative incorporates two pentacene units in addition to the initially installed single substituent (Fig. S32). Structural characterization of the isolated hetero-tris-adduct by NMR spectroscopy revealed that the two pentacene units occupy *equatorial* positions with respect to the mono-addend **2a** and adopt a *trans*-1 relative arrangement among them (full characterization in S28–S31). According to this *e*,*e*,*t*1 substitution pattern, two distinct isomers, denoted *e*,*e*,*t*1(*I*) and *e*,*e*,*t*1(*II*), are in principle possible (Fig. 2d), in agreement with previous reports on related systems.[16a] Careful analysis of the NMR spectra, together with conformational analysis of the fullerene-cage adduct, showed the formation of only one isomer, which was assigned to *e*,*e*,*t*1(*I*). In the 5–6 ppm region of the ^{1}H-NMR spectrum, four singlets integrating one proton each are observed and assigned to the C_{sp^3} protons of the reacted pentacene moieties. Two of these protons are oriented towards the mono-addend of **2a** and present different chemical shifts as a consequence of the stereocenter in the mono-addend, which renders them inequivalent. The remaining two protons are oriented towards the non-functionalized surface of the C_{60} and display closely spaced yet distinguishable resonances. Furthermore, NOESY experiments show no cross-peaks between the aromatic protons of the pentacene units and those of the phenyl of the **2a** addend. This observation is consistent with the *e*,*e*,*t*1(*I*) isomer, in which these protons are not in close spatial proximity; in contrast, the *e*,*e*,*t*1(*II*) isomer would be expected to exhibit such cross-peaks.

The sole formation of the *e*,*e*,*t*1(*I*) isomer can be rationalized by considering the orientation of **2a** addends within the **Cg**·$(BArF)_8$ nanocapsule. Encapsulation allows two possible orientations of the C–C bond linking the addend of **2a** to the

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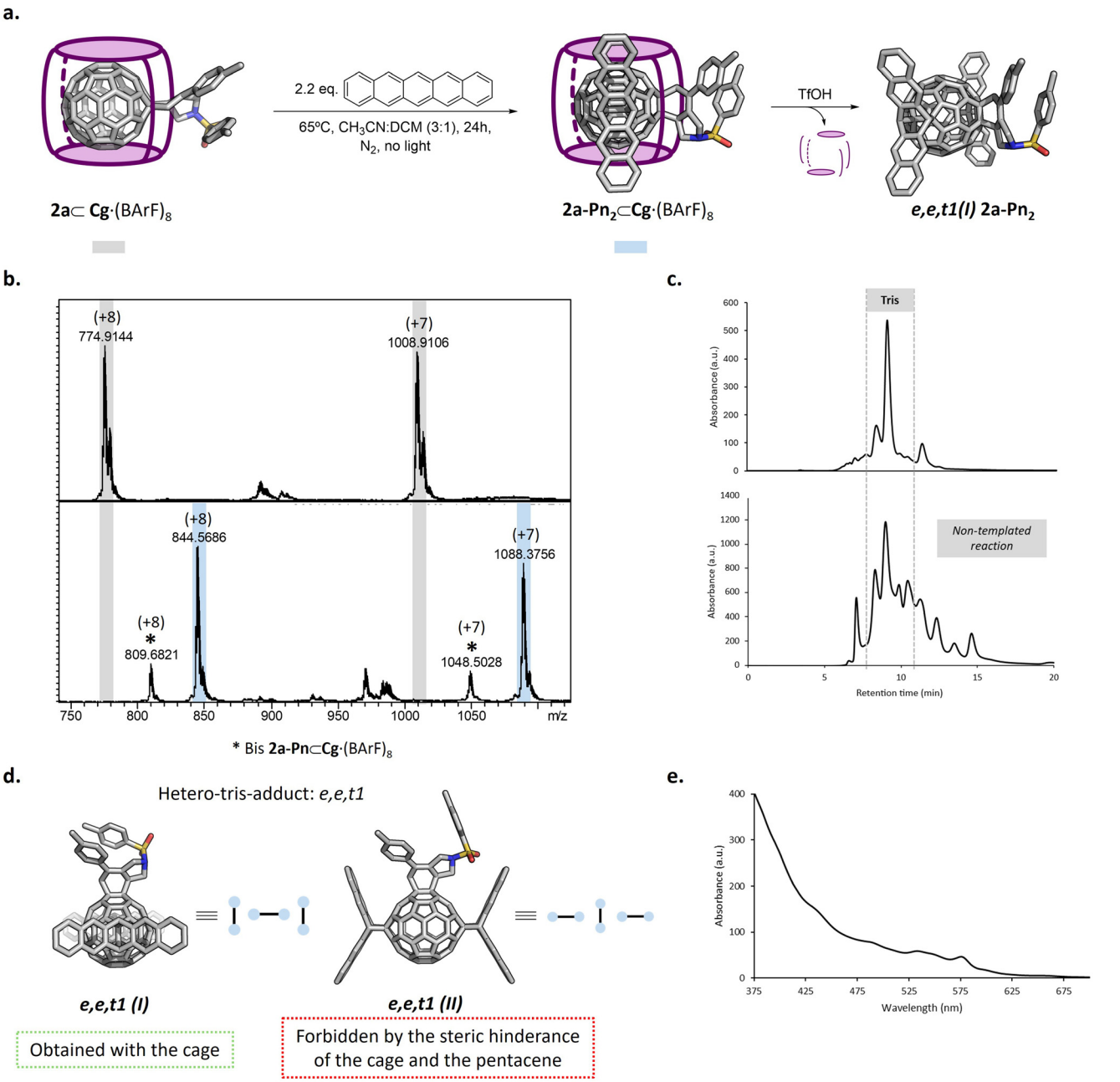

Fig. 2 (a) Synthesis of the hetero-tris-adduct *e,e,t*1(*I*) **2a-Pn$_2$**. (b) HRMS monitoring of the formation of *e,e,t*1(*I*) **2a-Pn$_2$**. (c) HPLC of the reaction crude in the presence of the nanocapsule (top) and in the absence of the nanocapsule (bottom). (d) Representation of the two possible isomers of the **2a-Pn$_2$**. (e) Absorption spectrum of the isolated *e,e,t*1(I) **2a-Pn$_2$**.

C_{60} core, namely vertical or horizontal with respect to the porphyrin panels of the cage. When the bond adopts a vertical orientation, the two *equatorial* bonds exposed through the contiguous gates are oriented horizontally, thereby enabling the incoming pentacene units to approach in a vertical orientation that minimizes steric clashes with the cage, as was previously demonstrated in studies of Diels–Alder di-functionalization of the C_{60}.[16b] In contrast, when the mono-addend is oriented horizontally, the *equatorial* bonds exposed through adjacent gates are vertical, which hinders the approach of pentacene in a horizontal orientation relative to the porphyrin units and is therefore sterically disfavoured. Consequently, the nanocapsule exclusively promotes the formation of the *e,e,t*1(*I*) isomer, effectively directing the reaction toward a single isomer. This assignment is also in agreement with the Molecular Dynamics simulations of the encapsulated **2a⊂Cg**·$(BArF)_8$ (Fig. S43).

To assess the role of the cage in controlling the reaction outcome, a control experiment was performed by conducting the Diels–Alder reaction of pentacene with mono-adduct **2a** in the absence of the cage. Owing to the poor solubility of the

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fullerene in acetonitrile (the solvent used with the reaction inside the cage), the reaction was carried out in toluene while maintaining identical reaction conditions. HPLC analysis of the crude reaction mixture revealed a complex profile, with multiple peaks corresponding to a mixture of poly-adducts and their regioisomers (Fig. 2c bottom and Fig. S33). Notably, in the absence of the cage, the mono-adduct **2a** is still present, and a significantly higher proportion of poly-adducts is observed, together with a much broader distribution of regioisomers. These results highlight the key role of the cage as a supramolecular mask, enabling control over both the number of substituents added to the fullerene surface and the regioselectivity of the fullerene modification.

Diels–Alder reaction with pentacene on the 2d mono-adduct

The same reaction protocol was subsequently applied to a second selected mono-adduct, *i.e.* **2d**. The reaction was carried out using 2.2 eq. of pentacene at 65 °C, with a cage concentration of 10^{-3} M in a MeCN : DCM (3 : 1) solvent mixture under N_2 atmosphere in the dark (Fig. 3a). HRMS monitoring revealed that after 24 hours, the bis-adduct was the predominant species. Upon extending the reaction time to 48 hours, only trace amounts of the bis-adduct remained, while the corresponding tris-adduct was identified as the major product (Fig. S34).

Following nanocapsule disassembly and work-up, HPLC analysis displayed a main peak, whose absorption spectrum is consistent with the *e*,*e*,*t*1(*I*) tris-adduct, along with additional peaks corresponding to other functionalized fullerenes patterns (Fig. 3b, d and S35; main peak at R_t = 9.7 min, other peaks: R_t = 10.8 and 8.8 min). No unreacted **2d** mono-adduct was detected. Purification of the main product was successful, affording the tris-adduct **2d-Pn$_2$** in a 38% isolated yield, determined by HPLC using C_{60} as internal standard. HPLC and absorption analysis of the isolated tris-adduct show spectral features comparable to those of *e*,*e*,*t*1(*I*) **2a-Pn$_2$** (Fig. S27 and S35).

The isolated tris-adduct was further characterized by ^{1}H-NMR spectroscopy (Fig. 3c and full characterization at S36 and S37). The pattern of the C_{sp3} protons of the pentacene moiety exhibits a 2 : 1 : 1 splitting rather than the expected 1 : 1 : 1 : 1, likely due to overlap of two proton signals, as suggested by the observed broad peak. Nevertheless, since both products obtained from **2a** and **2d** display identical absorption spectra, indicating identical substitution pattern on C_{60}, this isomer is assigned as *e*,*e*,*t*1(*I*) **2d-Pn$_2$**.

Similarly, as in **2a**, a control experiment was performed by reacting **2d** with pentacene in the absence of the cage (in toluene due to the insolubility of **2d** in acetonitrile). HPLC analysis of the reaction crude revealed multiple peaks (Fig. 3b bottom and S40), indicating a lack of selectivity with respect to both the number of pentacene moieties added and the formation of a mixture of regioisomers.

Diels–Alder reaction with pentacene on the 2e mono-adduct

The last compound to which we applied the SMS was **2e**. The reaction conditions were analogous to those used for **2d**.

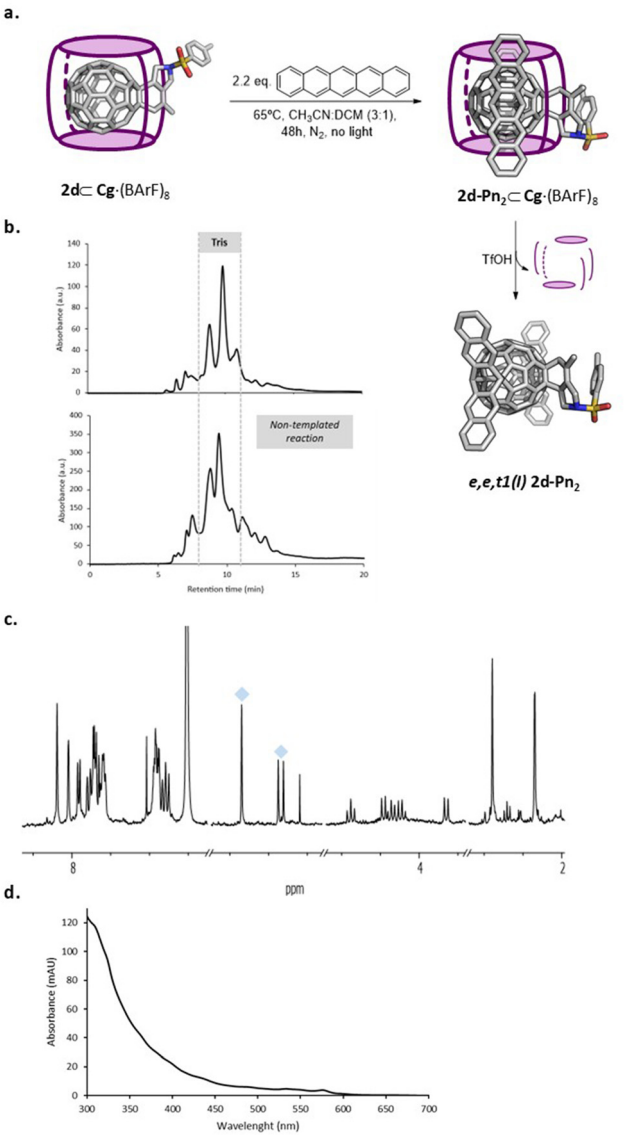

Fig. 3 (a) Synthesis of the hetero-tris-adduct *e*,*e*,*t*1(*I*)-**2d-Pn$_2$**. (b) HPLC of the reaction crude in the presence of the nanocapsule (top) and in the absence of the nanocapsule (bottom). (c) ^{1}H-NMR spectrum of the isolated *e*,*e*,*t*1(*I*) **2d-Pn$_2$**. Peaks of the C_{sp3}–H of the pentacene are labelled with a blue rhombus. (d) Absorption spectrum of the isolated *e*,*e*,*t*1(*I*) **2d-Pn$_2$**.

HRMS monitoring indicated that, after 48 hours, the tris-adduct was identified as the major product (Fig. S41).

Following nanocapsule disassembly and workup, the crude mixture was analysed by HPLC, revealing five distinct peaks (Fig. S42). These were assigned, from longest to shortest retention time, as follows: (i) is unassigned, which was already present in the starting mono-adduct (as observed in the HPLC of the mono-adduct); (ii) a small amount of unreacted mono-adduct; (iii and iv) two new peaks at 8.9 min and 7.8 min, both displaying absorption patterns consistent with functionalized fullerenes, and (v) pentacene. Attempts to isolate the tris-adduct were hampered due to strong interactions between the

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fullerenes and silica. Unexpectedly, the extraction of fullerene species from silica was challenging, yielding only small recoverable quantities of degraded compounds. Nevertheless, HRMS analysis of the reaction crude suggests a similar control of the regioselectivity in the tris-adduct product formed.

Conclusions

In summary, the selective hetero-tris-functionalization of fullerene using Diels–Alder cycloadditions in a sequential strategy is achieved. A first addend is introduced onto the fullerene through a cascade process involving a Ru-catalyzed cycloisomerization of 1,6-enynes followed by a Diels–Alder reaction with C_{60}. Subsequently, nanocapsules are employed as supramolecular masks to obtain higher levels of regioselectivity towards a Diels Alder hetero-tris-adduct containing two pentacene units positioned *equatorially* with respect to the initial addend and in a *trans*-1 relative orientation. In this manner, pure tris-regioisomers *e*,*e*,*t*1(*I*) **2a-Pn$_2$** and *e*,*e*,*t*1(*I*) **2d-Pn$_2$** are obtained in good yields. The nature of the initial substituent in **2** influences the formation of the hetero-tris-adducts: bulkier addends (**2a** > **2d**) provide improved regioselective control, favouring the formation of the *e*,*e*,*t*1(*I*) isomer while minimizing other hetero-tris-adducts. Moreover, **2a** forms the corresponding hetero-tris-adduct within 24 hours, whereas **2d** and **2e** require 48 hours to achieve comparable formation. This behaviour is attributed to the stronger confinement of the bulkier mono-adduct within the **Cg**·$(BArF)_8$ cage, which facilitates a more efficient and regioselective addition of pentacene. Overall, the cage enables control over both the degree of functionalization of the fullerene surface and the regioselectivity of the addition. Access to pure-isomer hetero-tris-DA-adducts is unprecedented and demonstrates the broad potential of the supramolecular mask strategy.

Author contributions

The manuscript was written with contributions from all authors. All authors have approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: detailed synthetic procedures and complete characterization data for all new compounds. See DOI: **https://doi.org/10.1039/d6qo00263c**.

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