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Alternatively Modified Bingel Reaction for Efficient Syntheses of C₆₀ Hexakis-Adducts

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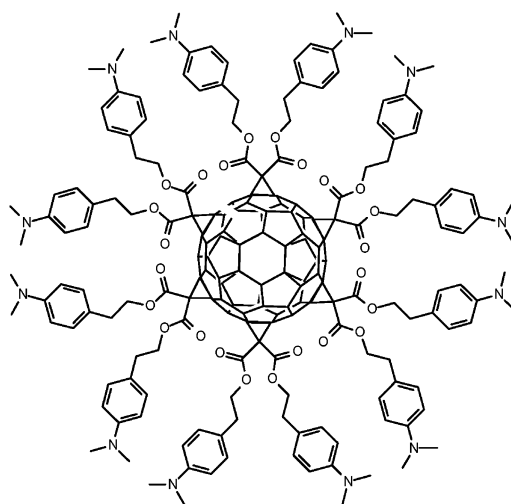
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ABSTRACT



It was found that the C₆₀ hexakis-adduct (*T_h*) bearing 12 electron-donating *N,N*-dimethylaniline moieties could not be synthesized by the Bingel–Hirsch method with either classical or deviated experimental parameters in a one-pot reaction. A different modification to the original Bingel reaction without the use of any templating agent was necessary for high-yield synthesis of the compound. The generalization of this alternatively modified Bingel method to the preparation of other C₆₀ hexakis-adducts is demonstrated.

Hexakis-adducts of fullerene C₆₀ represent a unique class of three-dimensionally symmetric (*T_h*) macromolecular structures,^{1–5} with nanoscale dimensions and stoichiometrically

defined chemical compositions. Their interesting properties as materials and their biocompatibility and potential biological applications have received much recent attention.^{6–8}

Most of the available C₆₀ hexakis-adducts bear the Bingel methano addition pattern.^{5,9,10} However, the original Bingel reaction conditions⁹ were found to be generally ineffective

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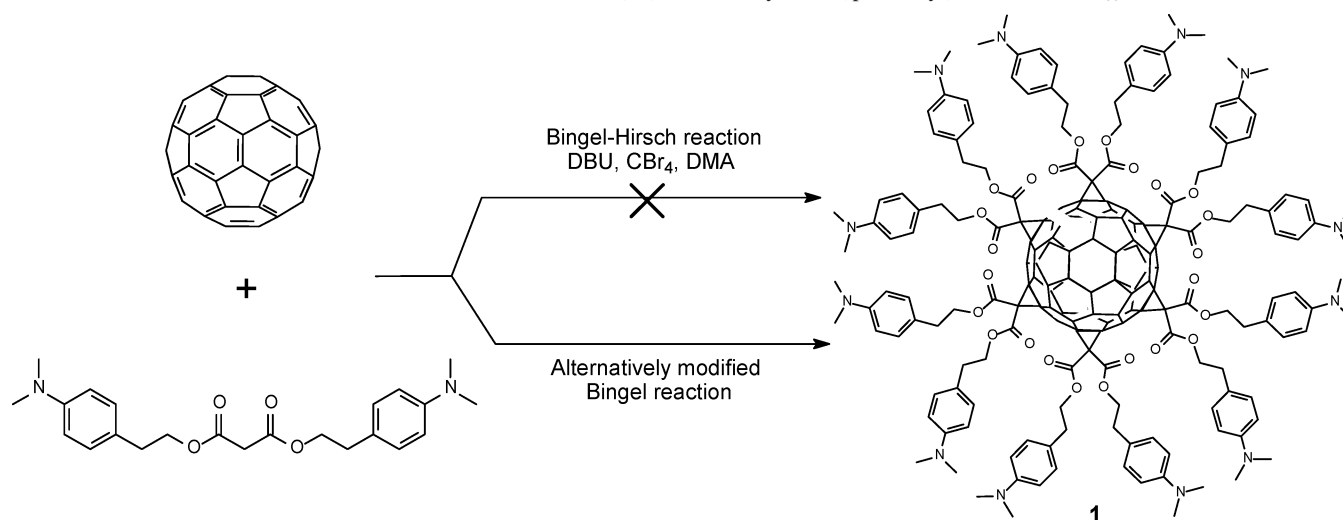
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Scheme 1. Hexakis-Addition of Bis(4-(*N,N*-dimethylamino)phenethyl) Malonate to C₆₀



in the hexakis-addition, and the modification by Hirsch and co-workers to include a templating agent such as 9,10-dimethylantracene in one-pot addition reactions has since become classical.⁵ The modified Bingel (often called the Bingel–Hirsch method) has generally been successful for relatively simple hexakis-adducts, such as those from the addition of dialkyl malonates, with yields up to 50–60%.^{5,10–12} For structurally more complicated hexakis-adducts, the Bingel–Hirsch reaction conditions suffer from generally low product yields or even negligible yields in some cases.^{5,6,12,13} For example, the yields in the hexakis-addition of first- and second-generation trisubstituted benzene-based dendra to C₆₀ were 5.4% and 2%, respectively.¹³ Recently, it was shown that a relatively simple deviation from the classical Bingel–Hirsch reaction parameters could improve substantially the yields in the one-pot preparation of C₆₀ hexakis-adducts bearing 12 tethered pyrene moieties,¹² suggesting that there is still great potential in further developing the hexakis-addition method to efficiently produce C₆₀-centered *T_h*-symmetric macromolecules of diverse tethers and functionalities.

In the synthesis of the C₆₀ hexakis-adduct bearing 12 electron-donating *N,N*-dimethylaniline units (**1**), we found that the compound could not be made in a meaningful yield by the Bingel–Hirsch method with either the classical or deviated experimental parameters. A different modification to the original Bingel reaction without the use of any templating agent was necessary for high-yield synthesis of the compound. The generalization of this alternatively modified Bingel method to the preparation of other C₆₀ hexakis-adducts is demonstrated.

For the addition, bis(4-(*N,N*-dimethylamino)phenethyl) malonate was synthesized and fully characterized. Despite repeated attempts, however, the classical Hirsch modification to the Bingel reaction with 9,10-dimethylantracene as the templating agent (Scheme 1) resulted in no detectable yield of the targeted compound **1**. Instead, the compound was readily synthesized in a different modification to the original

Bingel reaction with the use of a larger excess of carbon tetrabromide but without any templating agent (Scheme 1).

In a typical experiment, a solution of C₆₀ (36 mg, 0.05 mmol) in *o*-dichlorobenzene (10 mL) was prepared, and to the solution were added bis(4-(*N,N*-dimethylamino)phenethyl) malonate (200 mg, 0.5 mmol), CBr₄ (1.67 g, 5 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 150 mg, 0.1 mmol). The mixture was stirred for 24 h, followed by the removal of the solvent *o*-dichlorobenzene. The resulting sample was separated on a silica-gel column (chloroform with 3 vol % of pyridine as eluent) in a relatively straightforward fashion to obtain **1** (105 mg, 68% yield). The chemical structure of **1** was confirmed in terms of NMR and matrix-assisted laser desorption–time-of-flight (MALDI–TOF) MS analyses. Both ¹H and ¹³C NMR spectra (Figure 1) of the compound in CDCl₃ solution are characteristic of a hexakis-adduct of C₆₀.^{5,14} For example, the simple ¹³C NMR signals of only three peaks for the fullerene cage (145, 141,

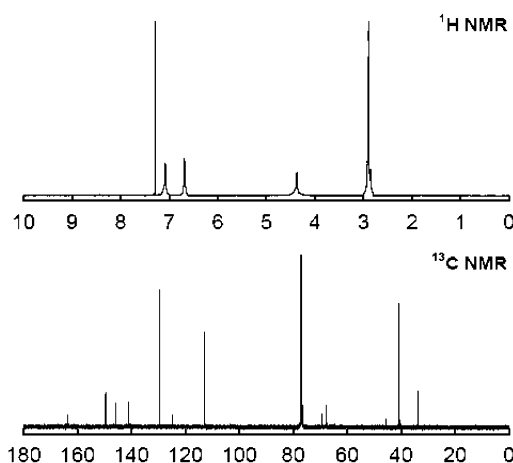


Figure 1. ¹H (top) and ¹³C NMR (bottom) spectra of **1**.

and 69 ppm) represent a classic indication for the high molecular symmetry (T_h). Shown in Figure 2 is a comparison

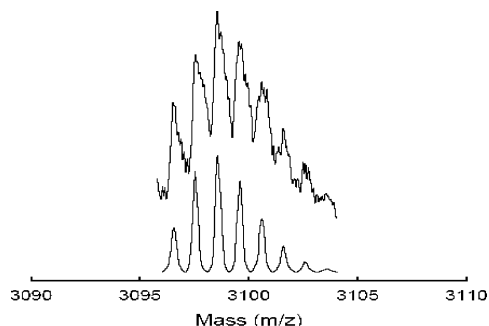


Figure 2. MALDI-TOF MS spectra of **1**: top (observed), bottom (calculated from IsoPro 3.0).

of the MALDI-TOF MS pattern of **1** with the prediction on the basis of isotopic populations (IsoPro 3.0). It is an excellent match, with the expected peak mass of 3097 Da ($C_{198}H_{168}O_{24}N_{12}$).

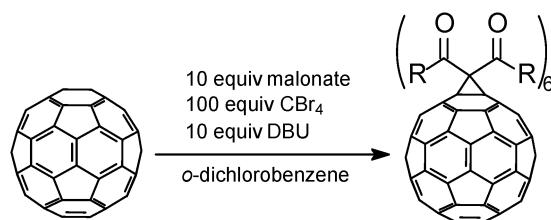
The successful synthesis of **1** in the absence of 9,10-dimethylantracene suggests that the use of a templating agent to activate and regulate the hexakis-addition onto the C_{60} core is hardly mandatory, as widely accepted in the literature. In fact, its presence impairs the hexakis-addition in the specific case shown in Scheme 1. This may be related to the fact that *N,N*-dimethylaniline moieties are strong electron donors, with their known redox interactions with the C_{60} cage in ambient solution.^{15,16} On the other hand, the large excess in CBr_4 obviously promotes the hexakis-addition, as also observed in the synthesis of other hexakis-adducts.¹² Even in the monoaddition experiment, the use of the same large excess in CBr_4 resulted in **1** in 15% yield instead of the intended monoadduct. Other control experi-

ments suggest that a lower concentration of either CBr_4 or DBU corresponds to a lower yield of **1**.

This alternatively modified Bingel reaction is applicable to the synthesis of other C_{60} hexakis-adducts that may or may not be obtained by the classical Hirsch modification. As shown in Table 1, the product yields are generally high.

Table 1. C_{60} Hexakis-Addition with Different Malonates

compound	—R	yield (%)
2		68
3		65
4		40



In summary, the alternatively modified Bingel reaction reported here is necessary for the synthesis of some structurally unique C_{60} hexakis-adducts. It at least complements the classical Bingel-Hirsch method for efficient one-pot hexakis-addition. With the demonstrated efficient synthesis of several C_{60} hexakis-adducts, the general applicability of the reported reaction to C_{60} hexakis-adducts that can otherwise be prepared by the classical Bingel-Hirsch method may be expected. Nevertheless, further investigations are required for a more systematic verification.

Acknowledgment. We thank Dr. M. E. Kose (Clemson U.) for experimental assistance. Financial support from NSF is gratefully acknowledged. M.T.-C. (Clemson U.) was a participant of the Summer Undergraduate Research Program sponsored jointly by NSF and Clemson University.

Supporting Information Available: Experimental procedures and spectral characterization for bis(4-(*N,N*-dimethylamino)phenethyl)malonate and hexakis-adducts **1–4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Simple Modification in Hexakis-Addition for Efficient Synthesis of C₆₀-Centered Dendritic Molecules Bearing Multiple Aromatic Chromophores

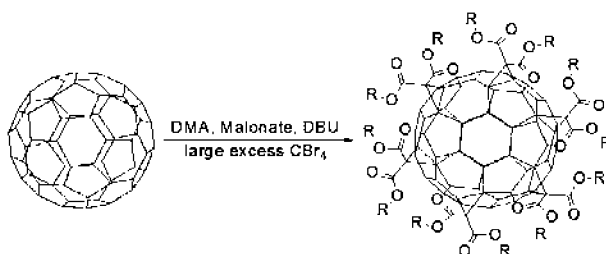
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ABSTRACT



In the templated hexakis-addition reaction of malonic esters with C₆₀ to prepare dendritic macromolecules that are terminated symmetrically with 12 derivatized pyrenes, a simple modification to use a much larger excess of the bromination agent resulted in dramatic increases in the product yields.

The highly symmetric molecule C₆₀ is considered to be an ideal core for dendritic molecular structures.^{1–3} In particular, C₆₀ can be functionalized in a highly symmetric fashion via templated hexakis-addition reactions.^{4–9} Several C₆₀-centered dendritic macromolecules have been synthesized.^{3,10–12} How-

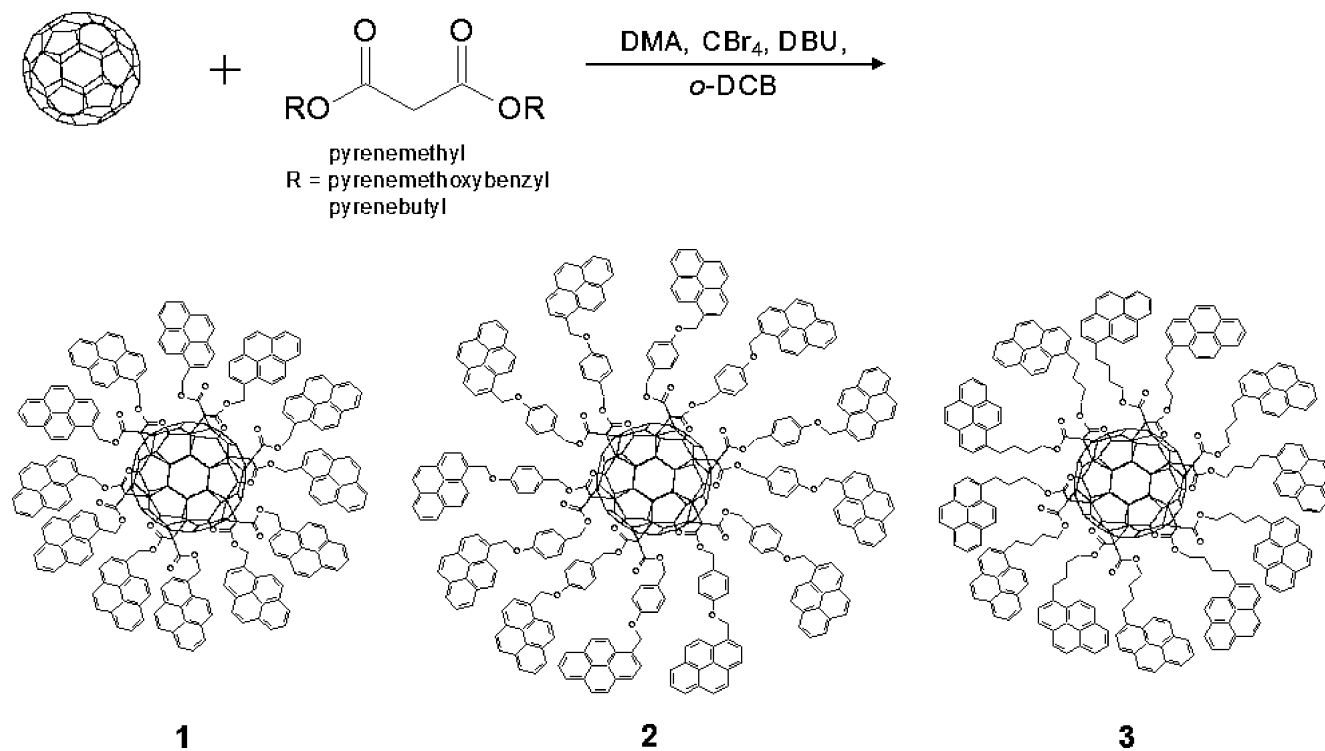
ever, the hexakis-addition of C₆₀ with bulky and/or complex functional groups typically suffers from low reaction yields, often only a few percent on the basis of consumed C₆₀.^{3,10–12} Because of the low yields, the separation of the desired hexakis-adducts from reaction mixtures is by no means a straightforward task. In our synthesis of the C₆₀-centered dendritic macromolecules bearing multiple aromatic chromophores (**1–3** in Scheme 1),¹³ we found a simple modification to the commonly used reaction conditions for the templated hexakis-addition of C₆₀ to achieve substantially improved product yields.

The malonic esters in Scheme 1 were prepared by using procedures similar to those already reported in the literature.¹⁴ The experimental details are provided in Supporting Information. The commonly used reaction conditions for the

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Scheme 1



templated hexakis-addition of C_{60} are generally the same as those originally reported by Hirsch and co-workers.^{7,8} These conditions were applied to the synthesis of compounds **1–3**. For compound **2**,¹³ as an example, the reaction conditions were to use *o*-dichlorobenzene as the solvent and to match the amount of C_{60} (0.05 mmol) with the templating agent 9,10-dimethylantracene at 10 equiv, the malonic ester at 10 equiv, carbon tetrabromide at 10 equiv, and the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 20 equiv. A product yield of 17% could be achieved.¹³ However, the same set of reaction conditions for the synthesis of **1** resulted in only a negligible amount of product, insufficient for any meaningful separation and isolation of the compound. On the other hand, while the synthesis of compound **3** under similar conditions was possible, with a comparable product yield of 16%, the compound was in a complex reaction mixture and thus very difficult to separate and especially challenging to obtain in a purified form.

In a search for better yields in the synthesis of **1–3**, we found that a simple modification to the commonly used conditions could substantially improve the hexakis-addition reactions. With such a modification of using a much larger excess of the bromination agent carbon tetrabromide, 5–10 times the usual amount, compound **1** could be synthesized and isolated in 10% yield, and the yields for compounds **2** and **3** were more than doubled.

For the synthesis of **1** under the modified reaction conditions, a solution of purified C_{60} (35 mg, 0.05 mmol) and 9,10-dimethylantracene (100 mg, 0.5 mmol) in *o*-dichlorobenzene (50 mL) was prepared and stirred for 5 h. To the solution was added bis(pyrenemethyl) malonate (266

mg, 0.5 mmol) and an excess amount of carbon tetrabromide (1.62 g, 5 mmol, 10 times that commonly used in the literature^{8,13}). The resulting solution was stirred for 30 min, followed by the addition of DBU (150 mg, 1 mmol). After constant stirring at room temperature for 8 days, the reaction mixture was filtered, concentrated, and separated on a silica gel column by using first hexane and then chloroform as eluents. The desired fraction in chloroform was concentrated and precipitated into hexane, and the precipitate was filtered and washed with acetone to obtain **1** as a yellow-colored solid (20 mg, 10% yield). The molecular structure of **1** was confirmed by results from both NMR and the matrix-assisted laser desorption ionization–time-of-flight (MALDI-TOF) MS characterizations.¹⁵ Apparently, the simple modification of using a much larger excess of the bromination agent while keeping other reaction parameters constant changed the preparation of **1** from being impossible to producing a decent yield.

Similarly, the large excess in carbon tetrabromide under otherwise the same reaction conditions increased the yield of compound **2** from 17 to 35%.¹⁶ For compound **3**,¹⁷ there was not only a more than doubling of the product yield to 40% but also a much improved separation and purification of the sample via conventional silica gel column chromatography. For the latter, we speculate that the modified

(15) ^1H NMR (500 MHz, CDCl_3) δ 7.95 (d, $J = 7.5$ Hz, 12H), 7.86 (d, $J = 7.5$ Hz, 12H), 7.80 (s, 12H), 7.76~7.65 (m, 48H), 7.57 (d, $J = 7.5$ Hz, 12H), 7.42 (d, $J = 7.5$ Hz, 12H), 5.57 (s, 24H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 163.18, 146.62 (cage sp^2), 141.96 (cage sp^2), 134.76, 134.27, 130.59, 129.39, 128.20, 127.93, 127.84, 127.53, 127.27, 126.01, 125.49, 125.42, 124.75, 124.24, 122.37, 120.09, 70.04 (cage sp^3), 67.04, 46.48 ppm; MALDI-TOF MS (M^+) 3904.

reaction conditions might be against the formation of byproducts with similar molecular structures to that of the hexakis-adduct (such as pentaadducts), which thus made it easier to isolate the compound from the reaction mixture.

There are generally speaking a limited number of C₆₀ hexakis-adducts available in the literature, with hardly any C₆₀-centered dendritic macromolecules symmetrically functionalized with multiple chromophores for comparison. This is probably a result of the difficulty associated with hexakis-addition under the commonly used reaction conditions (which do not allow the preparation of **1**, for example). A summary of other C₆₀ hexakis-adducts with various functionalities, based on an exhaustive literature search, is provided in Supporting Information. Except for those of simple dialkyl malonic esters,^{8,18–23} the hexakis-adducts are always produced in low yields and are typically separated from their respective

reaction mixtures by using specialized HPLC techniques, reflecting the level of technical challenge and complexity. Thus, the simple modification reported here for substantially higher yields in the templated hexakis-addition of bulky and/or complex malonic esters may have broad implications in the synthesis of C₆₀-centered dendritic macromolecules with currently inaccessible functionalities.

Acknowledgment. We thank S. Kumar, B. Zhou, and R. B. Martin for experimental assistance. Financial support from NSF and the Center for Advanced Engineering Fibers and Films (NSF-ERC at Clemson University) is gratefully acknowledged. R.C. was a participant of the Summer Undergraduate Research Program sponsored jointly by NSF and Clemson University.

Supporting Information Available: Experimental details on the synthesis and characterization of the malonic esters and a summary of other C₆₀ hexakis-adducts with various functionalities. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) **Compound 2:**¹³ ¹H NMR (500 MHz, CDCl₃) δ 8.03~8.02 (m, 2H), 7.97 (d, *J* = 7.5 Hz, 12H), 7.89~7.81 (m, 72H), 7.09 (d, *J* = 8.5 Hz, 24H), 6.84 (d, *J* = 8.5 Hz, 24H), 5.41 (s, 24H), 5.15 (s, 24H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 163.70, 159.10, 145.87 (cage sp²), 141.10 (cage sp²), 131.33, 131.05, 130.57, 130.50, 129.47, 129.04, 127.86, 127.39, 127.19, 127.13, 126.69, 125.79, 125.20, 124.68, 124.45, 122.82, 114.79, 69.15 (cage sp³), 68.53, 68.36, 45.59 ppm; MALDI-TOF MS (*M*⁺) 5177.

(17) Purified C₆₀ (35 mg, 0.05 mmol) and DMA (100 mg, 0.5 mmol) were dissolved in *o*-DCB (50 mL). After the solution was stirred at room temperature for 5 h, carbon tetrabromide (1.62 g, 5 mmol) and bis-(pyrenebutyl) malonate (308 mg, 0.5 mmol) were added. The solution was stirred for another 30 min, followed by the addition of DBU (150 mg, 1 mmol). After reaction for 8 days, the solvent *o*-DCB was removed. The solid sample was separated on a silica gel column by using first hexane to remove DMA and then chloroform to isolate the hexakis-adduct. The chloroform fraction thus collected was concentrated and then precipitated into hexane. The precipitate was filtered and washed with acetone to obtain **3** as a yellow-colored solid (88 mg, 40% yield): ¹H NMR (500 MHz, CDCl₃) δ 7.98~7.82 (m, 96H), 7.50 (d, *J* = 7.5 Hz, 12H), 4.01 (t, *J* = 6.5 Hz, 24H), 2.95 (t, *J* = 7.5 Hz, 24H), 1.60~1.50 (m, 48H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 166.37, 145.90 (cage sp²), 141.10 (cage sp²), 135.90, 131.43, 130.89, 129.88, 128.59, 127.46, 127.28, 127.12, 126.63, 125.80, 125.10, 124.88, 124.77, 124.70, 123.20, 69.40 (cage sp³), 66.70, 45.65, 32.86, 28.44, 27.87 ppm; MALDI-TOF MS (*M*⁺) 4409.

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