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Synthesis of Highly Fluorescent BODIPY-Based Nanocars

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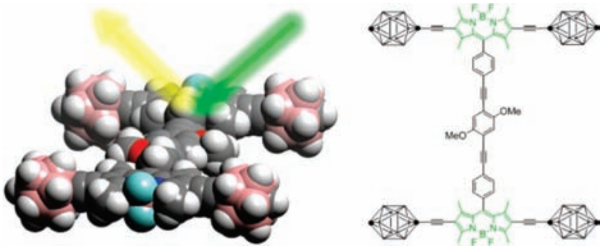
ABSTRACT



The convergent synthesis of inherently highly fluorescent nanocars incorporating 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY)-containing axles and *p*-carborane wheels is reported. These nanocars are expected to exhibit rolling motion with predetermined patterns over smooth surfaces, depending on their chassis. Their quantum yields of fluorescence ($\Phi_F > 0.7$) make them excellent candidates for imaging and tracking by single-molecule fluorescence microscopy. An analogue as a stationary control with *tert*-butyl groups instead of *p*-carborane wheels was also synthesized.

The control of motion at the molecular level stands as a challenge for scientists. Nature gives the supreme example of such control when the synchronization of motion of individual molecules leads to intricate biological functions.[1] Unfortunately, the use of natural molecular machines for *ex vivo* applications is intrinsically limited due to unfavorable environmental perturbations.[2] Much effort has been devoted toward the design, synthesis and operation of synthetic molecular machines. As a consequence, a large variety of nanostructures have been made to operate either in solution, in the solid state or mounted on surfaces.[3]

Our group has focused on the study of restricted rolling motion to control the translation of individual molecules along atomically flat surfaces. Incorporation of either C_{60}-fullerene,[4] *p*-carborane[5] or a ruthenium complex[6] as molecular wheels in a flexible oligo(phenylene ethynylene) (OPE) chassis has afforded a collection of molecular vehicles termed nanocars.[7]

Most nanocars were designed to be observed and tracked using scanning tunneling microscopy (STM) since it offers unparalleled atomic resolution.[8] Exploration of other single-molecule imaging tools, however, is essential in order to observe movement of nanomachines on nonconductive surfaces. Single-molecule fluorescence microscopy (SMFM) is a good alternative. Even though its resolution is limited by diffraction, nanometer localization of individual fluorophores has become possible.[9] Indeed, we recently reported the use of SMFM to monitor the motion of fluorescently tagged nanocars on a glass surface under ambient conditions.[10] The nanocars were functionalized with a tetramethylrhodamine fluorescent tag to allow excitation with a Nd:Vn laser (532 nm) and to have good

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quantum yields of fluorescence. The nanocars moved at an average speed of 4 nm/s at room temperature. However, the results suggested that the fluorophore might interfere with the nanocar motion by blocking some of the molecules. In addition, the synthesis of the tagged nanocars presented some drawbacks such as lengthy routes and low-yielding attachment of the fluorescent label. Consequently, a new set of intrinsically fluorescent nanocars was designed to obviate the need for a pendant fluorescent tag.

We report a modular and convergent synthesis of fluorescent nanocars **1**−**3** and the analogue **4** that incorporate a 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) core[11] in their axles. The BODIPY moiety is a versatile fluorophore; BODIPY-based chromophores tend to exhibit good thermal and photochemical stability, high fluorescence quantum yields, intense absorption profiles, tunability of absorption range, and good solubility in most organic solvents.[12] Furthermore, the geometry of the core yields nanocars where the chassis is perpendicular to the axles, leading to fewer conformations on the surface, in contrast to the previous 'Z-shaped' chassis obtained from OPE-axle-based nanocars.[5]

Nanocars **1** and **2** were designed to move in a straight line on surfaces while nanocar **3** is expected to exhibit circular surface motion that could be detected by measuring the polarization anisotropy distribution.[13] In order to confirm the importance of the *p*-carborane wheels in translational motion, nanocar analogue **4**, bearing *tert*-butyl groups instead of the *p*-carborane clusters, was also designed and synthesized.

Our synthetic strategy was based upon the realization that nanocars **1**−**3** (Figure 1) could be assembled by coupling two units of a BODIPY-containing axle with the appropriate inner portion or via a homocoupling. By incorporating the fluorophore in the axle, a modular synthesis of nanocars with various chassis is accessible. The *tert*-butyl-substituted analogue **4** could be analogously assembled using a different axle. Both axles were synthesized from known BODIPY **5**[14] using the 2,6-acetylenic functionalization first explored by Ziessel.[15]

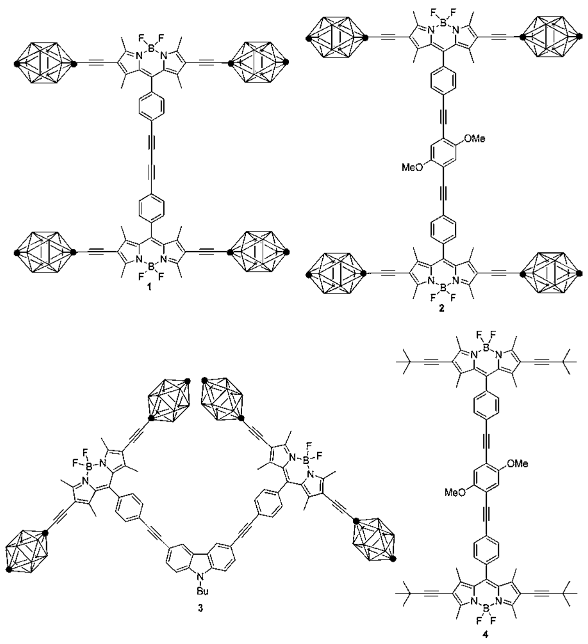
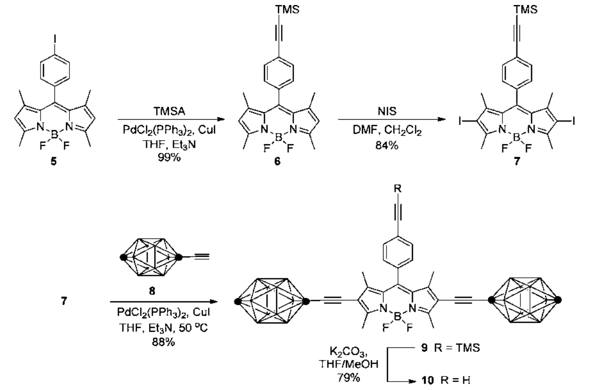


Figure 1. Structure of BODIPY-based nanocars **1**−**3** and analogue **4**. Every vertex of the carborane wheel is BH except the darkened sites, where the outer (para) is CH and the inner (ipso) is alkynyl-substituted C.

The synthesis of axle **10** (Scheme 1) started with a Sonogashira coupling reaction between BODIPY **5** and trimethylsilylacetylene (TMSA) that afforded **6**. Double iodination of the BODIPY core in **6** using *N*-iodosuccinimide (NIS) gave **7**. Diiodide **7** was then subjected to a double Sonogashira coupling with 1-ethynyl-*p*-carborane **8**[16] to give **9**, which upon TMS deprotection afforded axle **10**. Fluoride sources were avoided for deprotection since they are known to give lower yields due to partial destruction of the BODIPY core.[17] It is noteworthy that, in our experience, reaction times longer than 1.5 h with the K_2CO_3/MeOH system also reduce the yield and lead to formation of unknown byproducts. In summary, axle **10** was prepared in four steps from BODIPY **5** with an overall yield of 58%.

Scheme 1. Synthesis of Axle **10**



Nanocar **1** was assembled by palladium-catalyzed homocoupling of axle **10** in the presence of air (Scheme 2). The

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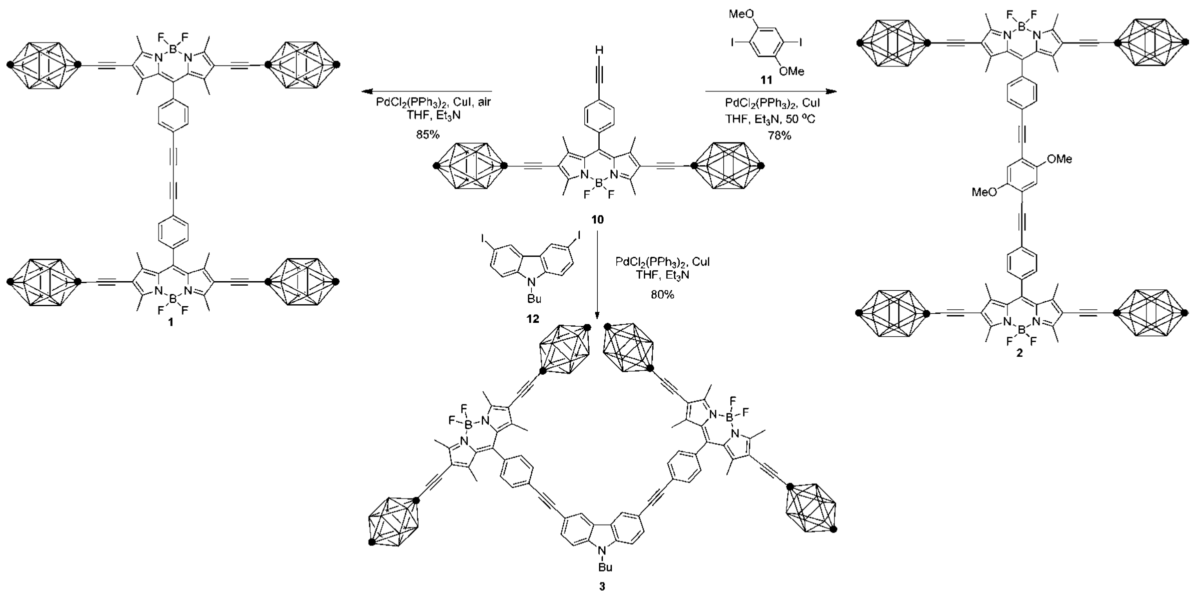
Scheme 2. Synthesis of Nanocars **1**−**3**

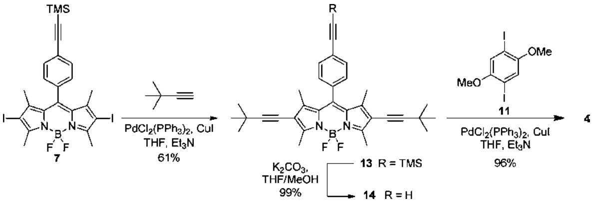


reaction was complete in 10 min, and the product was obtained in high yield. In contrast, Eglinton−Glaser conditions[18] led only to decomposition of **10**, probably due to substitution of the boron by the Cu(II) required in the process.[19]

Axle **10** was also used in the final assembly of nanocars **2** and **3** (Scheme 2). Synthesis of nanocar **2** was accomplished through Sonogashira coupling between 1,4-diiodo-2,5-dimethoxybenzene (**11**)[20] and 3 equiv of **10** to give **2** using typical coupling conditions. A methoxy-substituted benzene was used as the inner portion to allow easier purification away from the byproduct nanocar **1**. Similarly, to obtain nanocar **3**, 9-butyl-3,6-diiodo-9H-carbazole (**12**)[21] was coupled with 3 equiv of axle **10** to give the desired nanocar **3**.

In order to address the importance of the carborane wheels in translational motion, their replacement by a nonwheel-like group was desired. Introduction of small alkyl chains was considered since they are not expected to significantly modify the fluorescence of the BODIPY core. Lacking the wheel-like structure of *p*-carborane, an alkyl-substituted analogue would also enable us to evaluate the influence of the *p*-carborane on the absorption and emission properties of the BODIPY core. To prepare analogue **4**, bisiodide **7** was coupled with 3,3-dimethyl-1-butyne to give the TMS-protected axle **13**. After nearly quantitative deprotection, the free alkyne **14** was subjected to the final coupling with **11** to give the nanocar analogue **4** in excellent yield (Scheme 3).

Scheme 3. Synthesis of Nanocar Analogue **4**



The efficiency of the coupling reactions to obtain **1**−**3** suggests that the BODIPY-containing axle **10** is a versatile building block to prepare even more complex nanocars by varying the inner portion.

The optical properties of the nanocars and some precursors were investigated by UV−vis and fluorescence spectroscopy

Table 1. Optical Properties of all Compounds[a]

compd	λ_{abs} (nm)	ε (M^{-1} cm^{-1})	λ_{em} (nm)	Φ_F[b]
1	554	123 000	571	0.69
2	552	181 000	569	0.70
3	552	191 000	567	0.79
4	564	144 000	586	0.59
6	504	70 000	514	0.46
7	538	90 000	552	0.04
9	552	109 000	567	0.82
10	552	116 000	567	0.85
13	564	59 000	586	0.58
14	564	69 000	586	0.62

[a] Determined in chloroform solution, ca. 1×10^{-7} M. [b] Using rhodamine 6G as reference, $\Phi_F = 0.95$ in EtOH, λ_{exc} 488 nm. Excitation was done at the corresponding λ_{max} −30 nm..

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(Table 1). The photophysical behavior of some of the compounds reported here is particularly interesting, given that there is no previous report of carborane−BODIPY diads. The absorption spectrum of all compounds exhibit a strong $S_0 \rightarrow S_1$ ($\pi - \pi^*$) transition located between 504 and 564 nm with variable extinction coefficients depending on the substitution pattern. The molecules with two BODIPY units have the largest extinction coefficients due to the extension in the conjugated system. Interestingly, however, the *tert*-butyl-substituted compounds are slightly bathochromically shifted compared to their carboranyl-susbstituted analogues, probably due to the stronger electron-donating character of the *tert*-butyl groups.

Diiodo BODIPY **7** exhibits very low fluorescence quantum yield, in part due to efficient intersystem crossing caused by the heavy iodine atom, leading to a low-lying triplet state.[22] The fluorescence was restored, however, upon introduction of the alkynyl carborane wheels or the alkynyl *tert*-butyl groups and was retained after the final assembly. The presence of the carboranes enhanced the quantum yields (compare **10** with **14** and **2** with **4**). The fluorescence quantum yields of nanocars **1**−**3** are slightly smaller than that of the BODIPY axle **10** possibly due to partial through-bond energy transfer between the two BODIPY units. Since our current SMFM setup requires excitation of the molecules with a 514 nm laser, it was a prerequisite for the nanocars to exhibit reasonable absorption at this wavelength. As depicted in Figure 2, both nanocars and analogue (**1**−**4**) absorb in this region. Furthermore, the high fluorescence quantum yields of 69%, 70%, and 79% for nanocars **1**, **2** and **3**, respectively, make them particularly well-suited for imaging by SMFM at the excitation wavelengths.

In summary, the synthesis of three BODIPY-containing highly fluorescent nanocars and one analogue was achieved using a modular approach that involves a versatile BODIPY-containing axle. The nanocars were prepared in five steps with overall yields of 49%, 45%, and 46% for **1**, **2**, and **3**, respectively. Electronic spectroscopic studies revealed that the nanocars exhibit absorption centered around 550 nm and have high fluorescence quantum yields which makes them suitable for SMFM experiments. Investigation of their motion by SMFM at room temperature on a glass surface is currently underway.

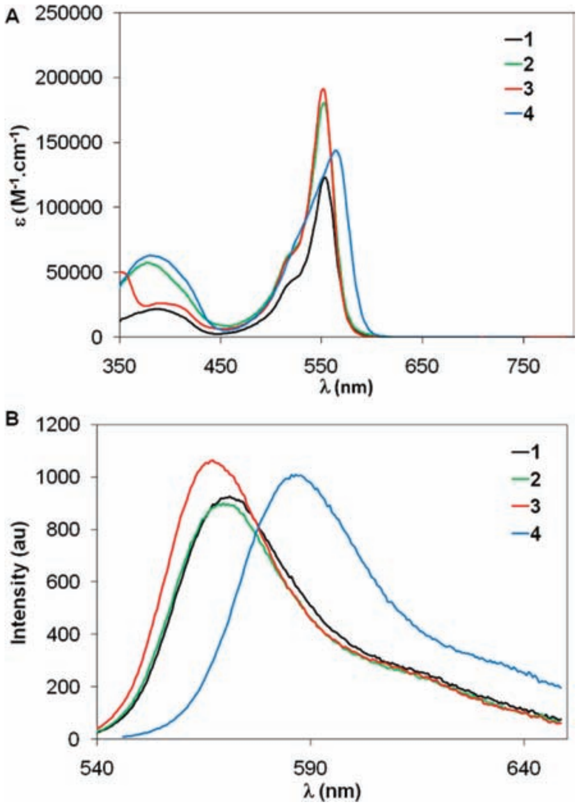

Figure 2. (A) UV−visible absorption spectra of **1**−**4** in $CHCl_3$. (B) Fluorescence spectra of **1**−**4** in $CHCl_3$. Excitation done at λ_{max} −30 nm.

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Supporting Information Available: Detailed experimental procedures and characterization of compounds **1**−**4**, **6**, **7**, **9**, **10**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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