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Letter

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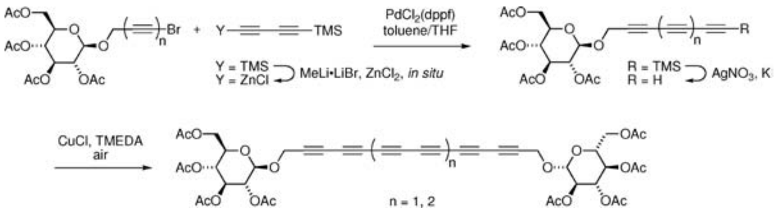

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A Convenient Negishi Protocol for the Synthesis of Glycosylated Oligo(ethynylene)s

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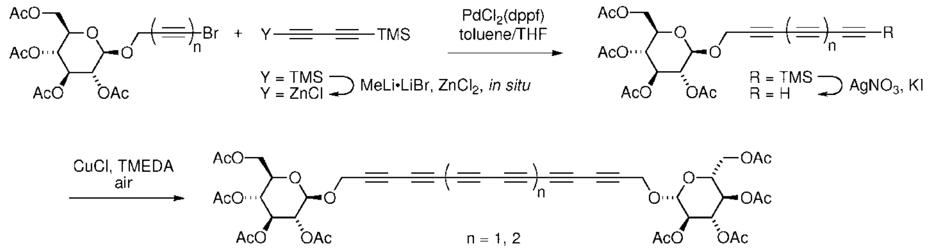
ABSTRACT



A convenient and efficient sp−sp carbon heterocoupling protocol based on the Negishi reaction was developed, in which the required zinc diacetylide was generated from 1,4-bis(trimethylsilyl)butadiyne in situ and reacted with a bromoacetylene in apolar solvent mixtures. The method has been applied to the synthesis of unsymmetric glycosylated and symmetric diglycosylated oligo(ethynylene)s up to the octa(ethynylene).

Oligo(ethynylene)s are intriguing targets both because of their nonlinear optical properties and as model compounds for the hitherto unknown carbon allotrope carbyne.[1−8] While most investigations to date have focused on stable derivatives, research in our own group aims at exploiting their inherent reactivity in order to use amphiphilic oligo(ethynylene)s as energy-rich molecular precursors for hierarchically structured carbon materials.

Although several protocols for the preparation and elongation of oligo(ethynylene)s exist,[9] the most commonly used methods remain the heterocoupling protocol according to Cadiot and Chodkiewicz[10] and the homocoupling reaction under Hay conditions.[11] While the former protocol has been applied in the synthesis of unsymmetric tri-, tetra-, and pentaynes,[6,12−15] the latter is often used as a final step and has allowed for the construction of molecules up to the hexadecayne.[6,15−17] Other synthetic pathways toward unsymmetric molecules have transferred typical Pd-catalyzed sp−sp^2 cross-coupling protocols to sp−sp carbon coupling reactions. For example, conditions analogous to the Sonogashira−Hagihara reaction[18] have proved to be very useful and were applied in the synthesis of oligo(ethynylene)s by several research groups.[19−23] The Negishi reaction, on the other hand, found

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(1) Szafert, S.; Gladysz, J. A. *Chem. Rev.* **2003**, *103*, 4175–4205.

(2) Dembinski, R.; Bartik, T.; Bartik, B.; Jaeger, M.; Gladysz, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 810–822.

(3) Diederich, F. *Nature* **1994**, *369*, 199–207.

(4) Lagow, R. J.; Kampa, J. J.; Wei, H.-C.; Battle, S. L.; Genge, J. W.; Laude, D. A.; Harper, C. J.; Bau, R.; Stevens, R. C.; Haw, J. F.; Munson, E. *Science* **1995**, *267*, 362–367.

(5) Schermann, G.; Grosser, T.; Hampel, F.; Hirsch, A. *Chem.—Eur. J.* **1997**, *3*, 1105–1112.

(6) Gibtner, T.; Hampel, F.; Gisselbrecht, J.-P.; Hirsch, A. *Chem.—Eur. J.* **2002**, *8*, 408–432.

(7) Eisler, S.; Slepkov, A. D.; Elliott, E.; Luu, T.; McDonald, R.; Hegmann, F. A.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2005**, *127*, 2666–2676.

(8) Luu, T.; Elliott, E.; Slepkov, A. D.; Eisler, S.; McDonald, R.; Hegmann, F. A.; Tykwinski, R. R. *Org. Lett.* **2005**, *7*, 51–54.

(9) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632–2657.

(10) Chodkiewicz, W.; Cadiot, P. *Compt. Rend.* **1955**, *241*, 1055–1057.

(11) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320–3321.

(12) Bohlmann, F.; Herbst, P.; Gleinig, H. *Chem. Ber.* **1961**, *94*, 948–957.

(13) Eastmond, R.; Walton, D. R. M. *Tetrahedron* **1972**, *28*, 4591–4599.

(14) Okada, S.; Hayamizu, K.; Matsuda, H.; Masaki, A.; Nakanishi, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 857–863.

(15) Bartik, T.; Bartik, B.; Brady, M.; Dembinski, R.; Gladysz, J. A. *Angew. Chem., Int. Ed.* **1996**, *35*, 414–417.

(16) Eastmond, R.; Johnson, T. R.; Walton, D. R. M. *Tetrahedron* **1972**, *28*, 4601–4616.

(17) Johnson, T. R.; Walton, D. R. M. *Tetrahedron* **1972**, *28*, 5221–5236.

(18) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.

(19) Wityak, J.; Chan, J. B. *Synth. Commun.* **1991**, *21*, 977–979.

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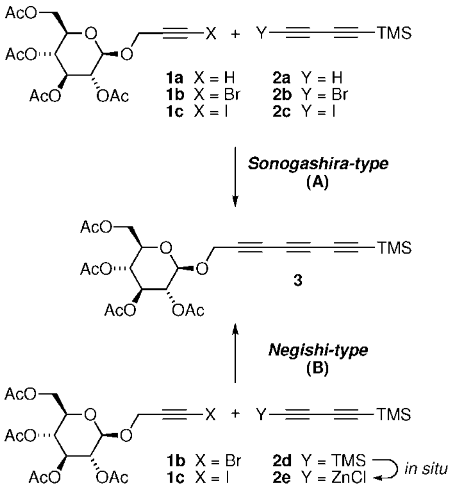
Scheme 1. Model Reaction for the Optimization of the Heterocoupling Reactions Analogous to the Sonogashira and Negishi Protocols[a]



[a]For detailed experimental conditions and yields, see Table 1.

entry into the synthesis of oligoynes by way of dehydrohalogenation of β-haloenynes.[24−26] However, the typical Negishi conditions have rarely been directly applied to sp−sp carbon cross-coupling reactions.[27−29] Commonly observed side products in all the heterocoupling protocols mentioned above are the homocoupling and the so-called selfcoupling products, which are formally derived from the mutual reaction of two terminal alkynes or two haloacetylenes, respectively. Tykwinski and co-workers devoted considerable effort to circumvent this problem and developed an alternative method for the synthesis of oligo(ethynylene)s based on the Fritsch−Buttenberg−Wiechel (FBW) rearrangement.[7,8,30,31]

In the present investigation, we developed a convenient and efficient sp−sp heterocoupling protocol on the basis of the Negishi reaction as a mild and copper-free alternative to existing protocols. For this purpose, different conditions analogous to the Sonogashira and Negishi coupling reactions were tested, varying the haloacetylene, the Pd catalyst, the solvent, and the reaction temperature. The generation of a zinc diacetylide from a stable trimethylsilyldiacetylene in situ, and its reaction with a bromoacetylene in an apolar solvent cleanly furnished the desired heterocoupling product in high yields. The optimized conditions were then used in the synthesis of carbohydrate-substituted oligo(ethynylene)s up to the octa(ethynylene) as potential amphiphilic, molecular precursors for a conversion into carbon materials.

Table 1. Results of (A) the Sonogashira-type and (B) the Negishi-type Coupling Reactions in the Synthesis of **3**

entry	method[a]	X (**1**)	Y (**2**)	conditions[c]	yield[d] (%)
1	A	H	I	a	23
2	A	H	I	b	14
3	A	H	Br	a	33
4	A	H	Br	b	35
5	A	H	Br	c	34
6	A	H	Br	d	22
7	A	I	H	a	16
8	A	Br	H	a	7
9	B	I	TMS[b]	e	23
10	B	I	TMS[b]	f	30
11	B	I	TMS[b]	g	40
12	B	Br	TMS[b]	g	26
13	B	Br	TMS[b]	h	48
14	B	Br	TMS[b]	i	80

[a] Sonogashira-type couplings (method A) and Negishi-type couplings (method B). [b] In the case of the Negishi couplings, the Zn-organyl was generated from bis(trimethylsilyl)butadiyne **2d** in situ by addition of MeLi·LiBr, followed by $ZnCl_2$ in THF; the obtained reaction mixture was then applied in the actual heterocoupling reaction. [c] Reaction conditions and reagents: (a) 2 mol % of $PdCl_2(PPh_3)_2$, 10 mol % of CuI, DIPA, THF, 0 °C; (b) 2 mol % of $Pd(PPh_3)_4$, 10 mol % of CuI, DIPA, THF, 0 °C; (c) 5 mol % of $PdCl_2(PPh_3)_2$, 10 mol % of CuI, DIPA, THF, 0 °C; (d) 3 mol % of Pd_2dba_3, 2.5 mol % of CuI, 0.2 equiv of LiI, 2.8 equiv of 1,2,2,5,5-pentamethylpiperidine, DMSO, rt; (e) 5 mol % of $Pd(PPh_3)_4$, THF, rt; (f) 5 mol % of $PdCl_2(dppf)$·DCM, THF, 0 °C; (g) 5 mol % of $PdCl_2(dppf)$·DCM, THF/toluene (3:7 v/v), rt; (h) 5 mol % of $PdCl_2(dppf)$·DCM, THF/toluene (3:7 v/v), 50 °C; (i) 10 mol % of $PdCl_2(dppf)$·DCM, THF/toluene (3:7 v/v), 0 °C. [d] Isolated yield of the heterocoupling product **3**.

In search of a suitable method for the synthesis of unsymmetric oligo(ethynylene)s, the FBW rearrangement was discarded because the conditions did not appear to be compatible with the presence of peracetylated glycosyl residues, and all attempts using the Cadiot−Chodkiewicz reaction had previously failed in our hands. Therefore, we decided to explore conditions analogous to both the Sonogashira and the Negishi coupling reactions, using the preparation of the glycosylated tri(ethynylene) **3** as a model reaction (Scheme 1, Table 1).

The Sonogashira-type reactions were carried out in tetrahydrofuran (THF) using different Pd catalysts, CuI as the cocatalyst, and an amine base (Table 1). However, none of these reactions furnished acceptable results. For example, the reaction of propargyl β-D-glucopyranoside **1a** and 1-iodo-4-trimethylsilylbutadiyne **2c** employing $PdCl_2(PPh_3)_2$, CuI, and diisopropylamine (DIPA) yielded 23% of the desired tri(ethynylene) **3** (entry 1). With $Pd(PPh_3)_4$ as the catalyst, the yield was even lower (entry 2). By comparison, reactions starting from 1-bromo-4-trimethylsilylbutadiyne **2b** furnished higher yields (entries 3 and 4), and the reaction with $Pd(PPh_3)_4$ as the catalyst resulted in the overall highest yield of 35% achieved with the Pd/Cu-promoted cross-coupling reactions. Increasing the catalyst concentration did not have a significant effect (entry 5), and,

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(20) Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 2053–2064.

(21) Lopez, S.; Fernandez-Trillo, F.; Castedo, L.; Saa, C. *Org. Lett.* **2003**, *5*, 3725–3728.

(22) Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, *6*, 3601–3604.

(23) Ding, L.; Olesik, S. V. *Nano Lett.* **2004**, *4*, 2271–2276.

(24) Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F. T. *J. Org. Chem.* **1984**, *49*, 2629–2632.

(25) Negishi, E.-i.; Hata, M.; Xu, C. *Org. Lett.* **2000**, *2*, 3687–3689.

(26) Metay, E.; Hu, Q.; Negishi, E.-I. *Org. Lett.* **2006**, *8*, 5773–5776.

(27) Negishi, E.-i.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597–1600.

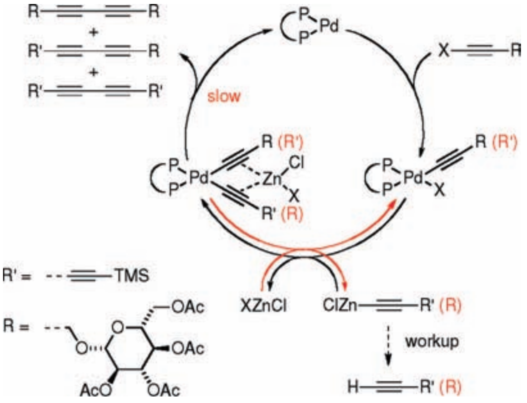
(28) Negishi, E.-I.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2017.

(29) Tykwinski and co-workers also performed a transmetalation of the lithium intermediate obtained via the FBW rearrangement into a zinc organyl in situ and coupled the latter to aryl halides as well as, in one example, 4-(2-iodoethynyl)toluene; see refs 30 and 31.

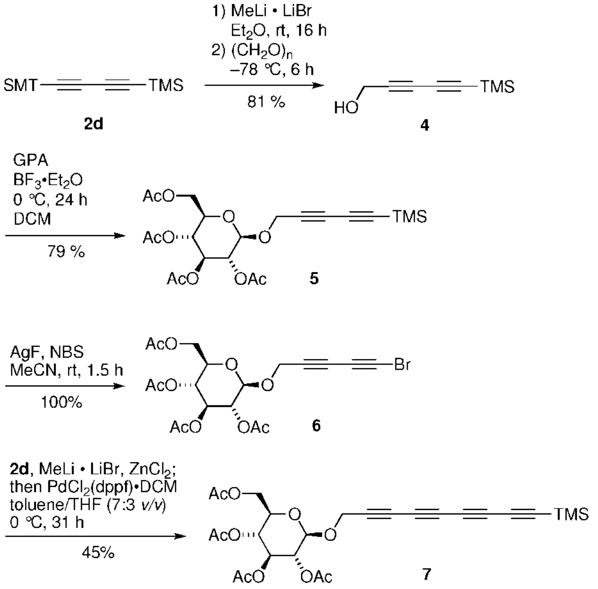
(30) Morisaki, Y.; Luu, T.; Tykwinski, R. R. *Org. Lett.* **2006**, *8*, 689–692.

(31) Luu, T.; Morisaki, Y.; Cunningham, N.; Tykwinski, R. R. *J. Org. Chem.* **2007**, *72*, 9622–9629.

Scheme 2. Slow Reductive Elimination and a Reversible Transmetalation in the Negishi Coupling May Explain the Observed Side Products, the Role of the Solvent, and the Advantageous Use of Bromoacetylenes



Scheme 3. Preparation of a Glycosylated Tetra(ethynylene) Using the Optimized Reaction Conditions Based on the Negishi Protocol



applying reaction conditions developed by Cai and Vasella,[20] the desired product **3** was obtained in a disappointing yield (entry 6). Despite the more acceptable results, the use of **2b** is unattractive since it is an unstable liquid which, reportedly, tends to explode upon heating,[32] rendering its purification dangerous. Finally, a permutation of the terminal acetylene and haloacetylene functionalities resulted in a yield of less than 20% starting from the 3-iodopropargyl β-D-glucopyranoside **1c** (entry 7) and decreased even further to an unacceptable 7% in the case of the 3-bromopropargyl β-D-glucopyranoside **1b** (entry 8).

The side product formation encountered in the Pd/Cu-promoted cross-coupling reactions turned out to be a serious issue. Thus, the homocoupling product was formed in large amounts in all cases and sometimes was the major product, despite the thorough exclusion of oxygen. Interestingly, the propargyl β-D-glucopyranoside **1a** was also observed as a side product in the reactions starting from the halopropargyl β-D-glucopyranosides **1b** and **1c** (entries 7 and 8), indicating that a reversible scrambling of the halogen substituents may be the origin of the generally unsatisfactory results (vide infra).

The limited success of the Sonogashira-type cross-coupling reactions led us to explore the scope of the Negishi protocol as an alternative because the diminished reactivity of alkynyl zinc compounds toward ester groups appeared to be compatible with the use of peracetylated glycosyl residues. Attempts to generate the essential alkynyl zinc derivative[33] **2e** from 1,4-bis(trimethylsilyl)butadiyne **2d** in situ,[29] using MeLi·LiBr in Et$_2$O for a selective monodesilylation[34] followed by addition of ZnCl$_2$ in THF, revealed that these two steps proceeded with quantitative conversion within minutes.[35] This rendered the Negishi protocol very attractive because the starting material 1,4-bis(trimethylsilyl)butadiyne **2d** is a stable crystalline compound, can straightforwardly be prepared on a 30 g scale, purified by sublimation, and stored at ambient conditions. The obtained solution of 4-(trimethylsilyl)butadiynyl zinc chloride **2e** in Et$_2$O/THF was then applied in the actual cross-coupling reaction following the Negishi protocol. Thus, with 3-iodopropargyl β-D-glucopyranoside **1c** as the substrate and 5 mol % of Pd(PPh$_3$)$_4$ as the catalyst in THF,[27] a yield of 23% of the desired tri(ethynylene) **3** was achieved (entry 9). The use of PdCl$_2$(dppf)·DCM as the catalyst increased the yield to 30% (entry 10) which can be attributed to an accelerated reductive elimination step. When the same reaction was conducted in less polar solvent mixtures such as toluene/THF (7:3 v/v), tri(ethynylene) **3** was already obtained in 40% yield (entry 11).[36] Comparable reactions starting from the 3-bromopropargyl β-D-glucopyranosides **1b** proceeded significantly slower but essentially without side product formation (entry 12).[37] While higher reaction temperatures led to increased reaction rates and substantially improved overall yields (entry 13), various side products were observed, and the reaction mixture turned black.

Therefore, the reaction was conducted in toluene/THF (7:3 v/v) at 0 °C but with an increased amount of catalyst (entry 14). Under these conditions, the reaction proceeded smoothly within a reasonable time frame. After 25 h, tri(ethynylene) **3** was isolated in a yield of 80%, and only traces of side products were observed. This excellent result combined with the convenient use of 1,4-bis(trimethylsilyl)butadiyne **2d** as the substrate render this protocol a valuable and efficient alternative to established procedures.

Interestingly, the propargyl β-D-glucopyranoside **1a** was, again, observed as one of the side products, and even as the major product when the reaction was conducted in polar

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[32] De Graaf, W.; Smits, A.; Boersma, J.; Van Koten, G.; Hoekstra, W. P. M. *Tetrahedron* **1988**, *44*, 6699–6704.

[33] Compound **2e** was already reported and used in a Pd-catalyzed propargylic 1,3-substitution; see: Kleijn, H.; Meijer, J.; Overbeek, G. C.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 97.

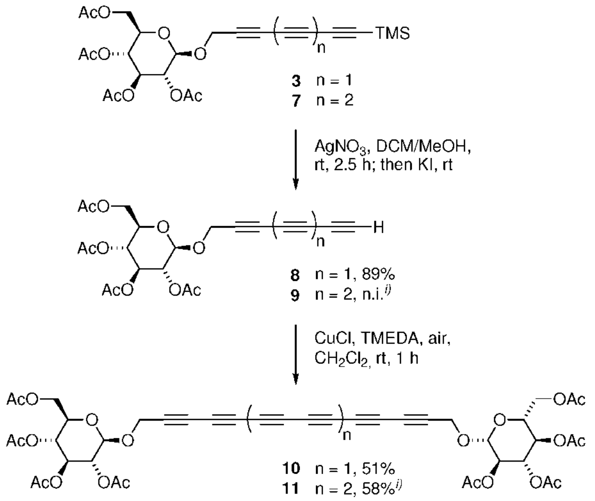
[34] Holmes, A. B.; Jones, G. E. *Tetrahedron Lett.* **1980**, *21*, 3111–3112.

[35] See the Supporting Information.

[36] THF can not be fully replaced as a solvent since it is indispensable in the preparation of the alkynyl zinc compound.

[37] At room temperature, a yield of 26% was achieved after 23 h reaction time, but only half of the starting material had reacted.

Scheme 4. Synthesis of the Symmetric, Diglycosylated Hexa(ethynylene) and Octa(ethynylene)



[i] Compound **11** was synthesized in 58% over two steps, since compound **9** was not isolable.

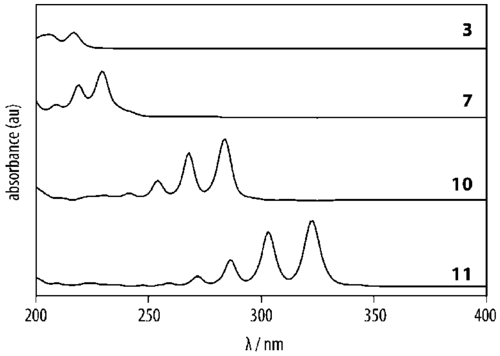


Figure 1. UV spectra of the oligo(ethynylene)s in acetonitrile.

solvents. Taking into account that the utilization of apolar solvent mixtures and bromoacetylenes as the substrates were the decisive modifications to achieve high conversions, we tentatively interpret these findings to result from both a rate-determining reductive elimination and, more importantly, a reversible transmetalation (Scheme 2). An equilibrium in the transmetalation may cause the observed scrambling of the reactant functionalities. Both the presumed homo- and self-coupling products may then be formed in heterocoupling reactions from the substrate mixtures. The use of bromoacetylenes in apolar solvents presumably leads to the formation of less soluble zinc salts and, thus, shifts the transmetalation equilibrium toward product formation.

The newly developed protocol based on the Negishi cross-coupling was then applied to the synthesis of higher glycosylated oligo(ethynylene)s (Scheme 3). Thus, the glycosylated diacetylene **5** was converted into the corresponding bromodiacetylene **6** according to a modified literature procedure.[22] The Pd-catalyzed coupling of **6** under the established conditions afforded the TMS-protected glycosylated tetra(ethynylene) **7** in 45% yield. The tri(ethynylene) **3** and the tetra(ethynylene) **7** were then desilylated using $AgNO_3$ in DCM/MeOH, furnishing the corresponding terminal acetylenes **8** and **9** (Scheme 4).

Table 2. Selected Optical Properties of the Glycosylated Oligo(ethynylene)s with *n*-Conjugated Triple Bonds

compd	n	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})
3	3	220	123000
7	4	232	355000
10	6	287	474000
11	8	326	504000

The tri(ethynylene) **8** was isolated in 89% yield and then subjected to an acetylene homocoupling under Hay conditions, furnishing the symmetric, diglycosylated hexa(ethynylene) **10** in 51% yield. As the tetra(ethynylene) **9** turned out to be highly unstable in the solid state, it was directly applied in the following Hay coupling after removing the silver iodide from the deprotection reaction with a silica gel filtration. The symmetric octa(ethynylene) **11** was obtained in 58% yield over two steps. Both **10** and **11** were stable at room temperature for days, at least, probably due to the sterically demanding carbohydrate end groups.

The UV absorption spectra of the oligo(ethynylene)s **3**, **7**, **10**, and **11** (Figure 1; Table 2) revealed the expected bathochromic shifts and hyperchromic effects upon increasing the number of conjugated triple bonds, as well as a very clearly resolved vibronic fine structure for the higher oligo(ethynylene)s. In comparison to other series of oligo(ethynylene)s with different end groups, such as disilyl[16] or diaryl[8] derivatives, the glycosylated CH_2O substituents induce significantly smaller bathochromic shifts with respect to the unsubstituted parent oligo(ethynylene)s.[16]

In conclusion, an efficient, convenient, and copper-free sp−sp heterocoupling protocol based on the Negishi reaction has been developed for the preparation of unsymmetric oligo(ethynylene)s. The required zinc acetylide was generated from the corresponding stable trimethylsilyl derivative in situ, and the use of an apolar solvent and bromoacetylenes furnished the desired heterocoupling product in high yield. The method was applied to the synthesis of unsymmetric glycosylated and symmetric diglycosylated oligo(ethynylene)s up to the octa(ethynylene). These compounds are important intermediates in the envisaged preparation of carbon-rich amphiphiles to be used as potential molecular precursors for hierarchically structured carbon materials.

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Supporting Information Available: Additional figures, experimental procedures, analytical data, and NMR spectra of all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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