Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Substituted [8]Cycloparaphenylenes by [2 + 2 + 2] Cycloaddition

Anne-Florence Tran-Van,[†] Elena Huxol,[†] Jonathan M. Basler,[†] Markus Neuburger,[†] Jean-Joseph Adjizian,[‡] Chris P. Ewels,[‡] and Hermann A. Wegner*[,§]

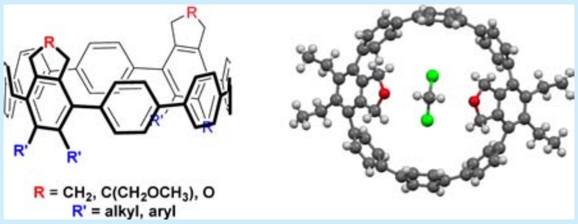
[†]Department of Chemistry, Basel University, St Johanns-Ring 19, CH-4056 Basel, Switzerland

[‡]IMN, CNRS, Université de Nantes, 2, rue de la Houssinière, BP32229, F-44322 Nantes, France

[§]Institut Organische Chemie, Justus-Liebig Universität, Heinrich-Buff-Ring 62, D-35392 Giessen, Germany

S Supporting Information

ABSTRACT: A new modular approach to the smallest substituted cycloparaphenylenes (CPPs) is presented. This versatile method permits access to substituted CPPs, choosing the substituent at a late stage of the synthesis. Variously substituted [8]CPPs have been synthesized, and their properties analyzed. The structural characteristics of substituted CPPs are close to those of unsubstituted CPPs. However, their optoelectronic behavior differs remarkably due to the larger torsion angle between the phenyl units.



Strained aromatic macrocycles have attracted the attention of chemists for over 80 years.[1] Recently, interest in cycloparaphenylenes (CPP) has increased dramatically, as they can be viewed as the shortest fragment of an armchair carbon nanotube (CNT). The development of an efficient entry into these compounds might allow the controlled preparation of CNTs from a CPP precursor.[2] Since the first synthesis of CPP in 2008,[3] several syntheses of various CPPs were proposed.[4] Interest for such molecules is not limited to the potential for CNT growth. Indeed, this class of molecules also finds applications for complexation[5] and possesses appealing characteristics itself. Their properties have been both theoretically and experimentally investigated.[3,4k,5b,6] In order to gain deeper insight into this class of strained molecules, it would be of great interest to study the effect of substituents on the properties of CPPs. Up to now very few substituted CPPs have been synthesized.[7] Therefore, we aim to provide a highly modular synthesis of substituted CPPs, allowing access to CPPs with different functional groups for further chemistry. Besides new host–guest possibilities, substituted CPPs could find applications in nanoporous materials with a defined pore size, and also as chemosensors.[8]

Initially, our strategy relied on a [2 + 2 + 2] cycloaddition reaction. The strain required should have been compensated by the aromaticity gained.[9] But unexpectedly, no attempt in this direction was successful. Therefore, a modified approach has been applied (Figure 1) still relying on a [2 + 2 + 2] cycloaddition reaction, as it allows introduction of substituents in a late stage of the synthesis. A building block containing methoxymethyl (MOM) protected cyclohexanediol units, suggested by Vögtle[10] and later by Hopf and Sankararaman[11] and recently applied by Itami,[4f,i,j,o] provided the required curvature.

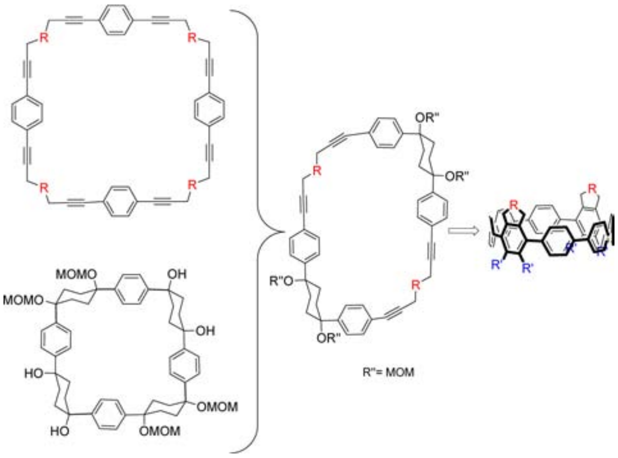
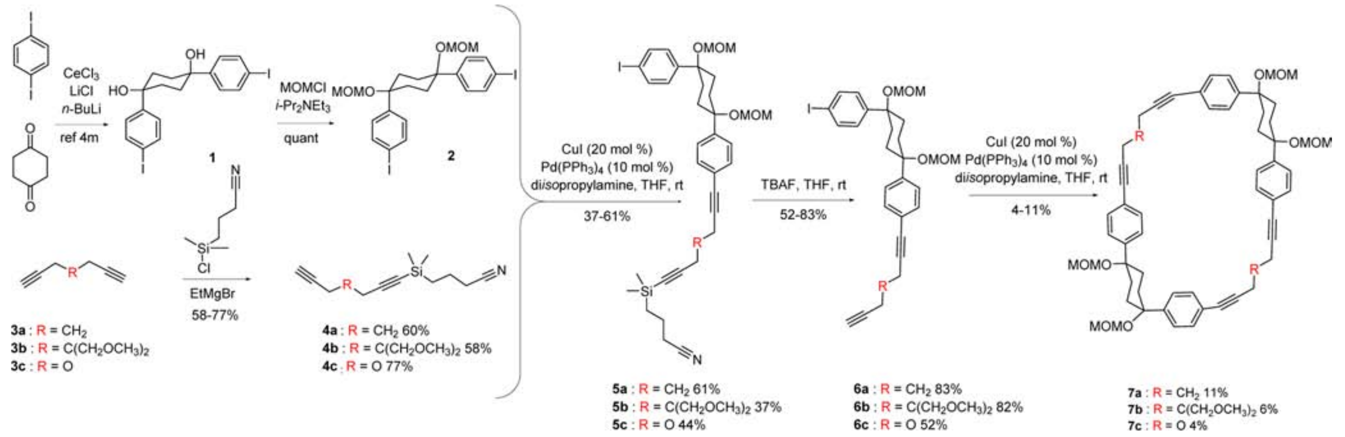


Figure 1. Strategy toward the synthesis of substituted CPPs.

Structure **2** (Scheme 1) was synthesized according to literature procedures.[4f,o] Building block **4** was obtained by protecting dialkyne **3** with (3-cyanopropyl)dimethylsilyl (CPDMS). This protecting group was chosen to facilitate the separation of the non-, mono-, and diprotected products obtained by this statistical reaction.[12] The two building blocks **2** and **4** were subsequently assembled via Sonogashira reaction producing differently substituted diynes **5** again in statistical yields. Deprotection of **5a–c** using TBAF furnished the key intermediates **6a–c** in moderate to good yields. Performing the reaction with K_2CO_3 in MeOH/THF led to partial degradation. With TBAF the reaction proceeded extremely fast. The

Received: January 20, 2014
Published: March 5, 2014

Scheme 1. Synthesis of the Macrocyclic Precursor



reaction required careful monitoring in order to be stopped before degradation occurred. This improved method was also amenable to a larger scale (12 mmol). With monomer fragments **6a**−**c** available, macrocycles **7a**−**c** were prepared by dimerization via Sonogashira coupling. Treatment of **6a**−**c** with Pd(PPh$_3$)$_4$ and copper iodide in THF (38 mM) in the presence of diisopropylamine generated the desired macrocycles **7a**−**c** in yields between 4 and 11%. Suspension in the ethylacetate/hexane mixture and filtration gave the pure product after an initial purification by column chromatography on silica. Halving the mixture concentration did not change the resultant yield. However, doubling the concentration dropped the yield to 2%. A single crystal was obtained and measured by X-ray spectroscopy. The solid state structure showed a unique rectangular shaped macrocycle shown in Figure 2a.

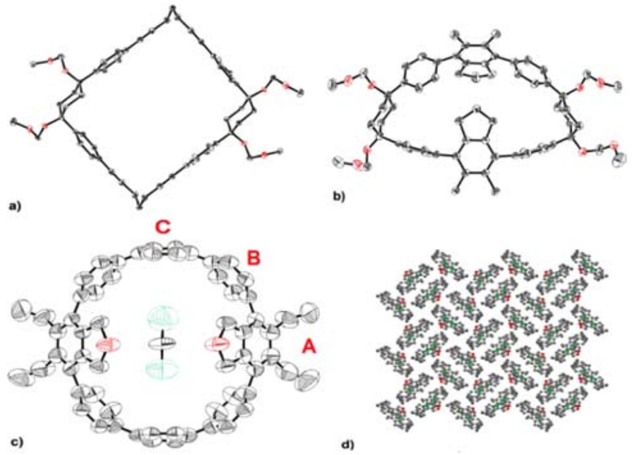
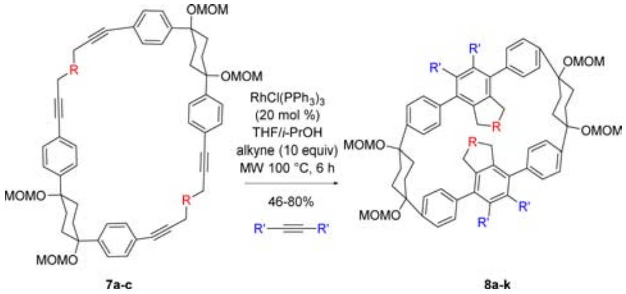


Figure 2. (a) Crystal structure of macrocycle **7a** (solvent omitted), (b) crystal structure of **8b** (solvent omitted), (c) crystal structure of **9d** (for a−c ORTEP drawings, hydrogen omitted), and (d) packing structure of **9d**.

Table 1. [2 + 2 + 2] Cycloaddition



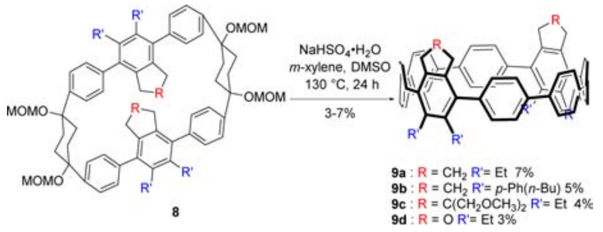
entry	product	R	R′	yield
1	**8a**	CH$_2$	Et	52%
2	**8b**	CH$_2$	Me	80%
3	**8c**	CH$_2$	Ph	67%
4	**8d**	CH$_2$	CH$_2$OH	56%
5	**8e**	CH$_2$	p-Ph(n-Bu)	54%
6	**8f**	CH$_2$	p-PhOCH$_2$CH$_2$OCH$_3$	47%
7	**8g**	CH$_2$	m-biph	74%
8	**8h**	O	Et	46%
9	**8i**	C(CH$_2$OCH$_3$)$_2$	Et	68%

We then investigated the [2 + 2 + 2] cycloaddition reaction on macrocycles **7a**−**c**. The reaction was performed under microwave irradiation (100 °C, 6 h) with Wilkinson's catalyst and an excess of alkyne. The results with various alkynes are summarized in Table 1. The reaction proceeded in moderate to very good yields. Purification was done by simple filtration and washing of the reaction mixture, affording easily the desired pure product. However, this method of purification cannot be applied with solid alkynes as they are used in excess. For this intermediate, a solid state structure was also determined (Figure 2b). The reaction proceeds for a wide range of precursors, offering a reliable method of functionalization for this type of molecule.

The final step of the synthesis of substituted CPPs involved deprotection−elimination and aromatization of macrocycle **8**. Various conditions were tried to achieve the target compound, based on the nonmicrowave conditions initially developed by Itami et al.[4m] Using sodium bisulfate in DMSO/m-xylene at 130 °C under air, the aromatization reaction produced the desired CPPs. Differently substituted CPPs were obtained with this method (Scheme 2). The larger torsion angle (see discussion below) could account for the low yield in this last step.

A suitable single crystal of **9d** was obtained by slow evaporation of a solution in dichloromethane and measured by X-ray spectroscopy (Figure 2c). In the solid state only the syn-isomer (R-groups on the same side of the ring) is observed. The ^{1}H NMR shows for all CPPs prepared sharp lines of only one species meaning that only one isomer is present as rotation is too high in energy according to preliminary calculations. The

Scheme 2. Aromatization Reaction



ring has a round shape with a diameter of 10.95 Å (average calculated between the *ipso*-bonds and the centers of the phenyl rings). This value is comparable to the diameter calculated for [8]CPP.[4k] Bond lengths are 1.400, 1.379, and 1.489 Å for C_{ipso}—C_{ortho}, C_{ortho}—C_{ortho}, and C_{ipso}—C_{ispo} bonds respectively, suggesting benzenoid character, as in the case for unsubstituted CPPs. In all CPPs phenyl rings are distorted. The angles between the normal benzene plane and the distorted out-of-plane atoms (α) respectively the C_{ipso}—C_{ispo} bond (β) display the degree of distortion. Those parameters were determined for a range of calculated CPP structures by Itami et al.[6b] In the substituted CPP **9d**, α equals 8.5° and β equals 14.4° which are comparable to the values for [8]CPP (α = 9.3°, β = 13.7°).[6b] The torsion angle between the middle unsubstituted ring **C** (Figure 2) and the other unsubstituted rings **B** is 32.8°, which is close to the value measured for [8]CPP.[6b] The angle between the substituted ring **A** and its adjacent rings **B** is 53.8°. This value is larger than that for unsubstituted CPPs. Based on these results, even less π-conjugation can be expected in substituted CPPs than the unsubstituted CPPs. Additionally, the packing arrangement is different from unsubstituted CPPs, where channels are sometimes observed. Here, pairs of rings arrange parallel to each other, and these pairs assemble forming a basket weave motif (Figure 2d).

The crystal structures of these three molecules illustrate the increasing strain of the molecules toward the end of the synthesis. The solid state structure of the macrocycle **7a** (Figure 2a) shows no deformation of the phenyl rings. However, in precursor structure **8b** (Figure 2b), most of the phenyl rings are already distorted with α = 3.7°. One ring shows a deviation from planarity similar to the case of the equivalent CPP. The torsion angle between most of the phenyl rings is 80.3° which is far more prominent than that for CPP. This is due to the remaining flexibility of the molecule.

Previous theoretical studies have calculated the structures and strain energies of CPPs using density functional theory (DFT) at the B3LYP/6-31G(d) level of theory. Strain energy was estimated via a homodesmotic reaction of CPPn and n biphenyls giving n *p*-terphenyls.[6g] However, we adopted a different approach to calculate the strain energy of **9**, which seems more appropriate to us, due to the fact that only the strain energy of the two relevant structures, the cyclic and the infinite linear PP, are calculated. This is achieved by breaking a bond in the CPP and straightening the fragment. This structure was placed in a repeating supercell so that the broken bonds connect to each other across opposite sides of the cell. This approach avoids any additional energetic terms due to changes in conjugation that may be present in the hypothetical homodesmotic reaction approach and is better adapted to substituted rings. With this method, via DFT optimization (see Supporting Information for details), the strain energy obtained was 63.7, 51.1, 73.6, and 62.4 kcal/mol for **9a**, **9b**, **9c**, and **9d** respectively. The results show that side-group functionalization can vary the ring strain within around ±11 kcal/mol from the unsubstituted [8]CPP ring strain (62.9 kcal/mol). This range is comparable with the change in ring strain from [6]CPP to [8]CPP.

The optical properties (UV−vis absorption and fluorescence) of the different substituted CPPs **9** were measured (Figure 3). The absorbance maxima (λ_{abs}) of the substituted CPPs lie between 301 and 312 nm (Table 2). These occur at shorter wavelengths than those for the corresponding unsubstituted [8]CPP (340 nm), which can be rationalized by the larger torsion angle compared to that for unsubstituted CPPs. Extinction coefficients are also considerably smaller than that for [8]CPP.[4k] The emission maxima (λ_{em}) were observed between 451 and 465 nm (Table 2). These values are again smaller than that for the unsubstituted [8]CPP (540 nm).[6b] The absolute fluorescence quantum yields were measured in chloroform using a calibrated integrating sphere. These yields are smaller than those measured for [9]CPP using the same method,[6b] indicating an influence of the substitution on the photoluminescence pathways. With these values our CPPs fit perfectly into the expected range. They match the trend among CPPs synthesized to date, namely the larger the diameter and the larger the distortion due to substitution, the lower the emission wavelength.[4k,6b]

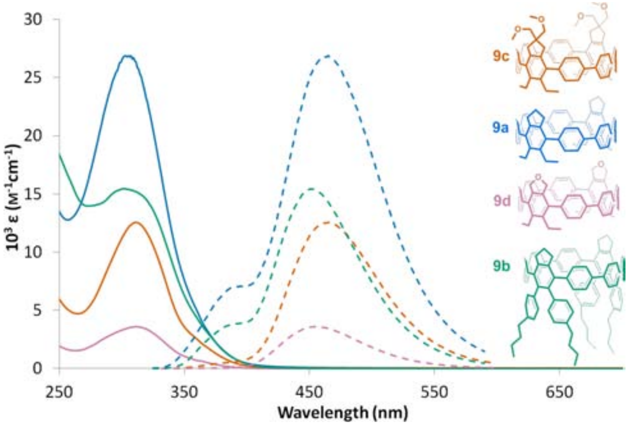


Figure 3. UV−vis absorption (solid lines) and fluorescence spectra (dashed lines) of substituted CPPs **9a−d**. The fluorescence was normalized to the absorption maximum (measured in chloroform 10^{-4} M).

Table 2. Photo-optical Properties of Substituted CPPs

	λ_{abs} (nm)	λ_{em} (nm)	quantum yield	fluorescence lifetime (ns)
9a	306	465	0.24	3.5
9b	301	451	0.06	3.3
9c	312	465	0.36	3.7
9d	312	453	0.46	4.3

In conclusion, using a [2 + 2 + 2] cycloaddition reaction as the key step allowed us to synthesize the smallest substituted CPPs in a highly modular way. The advantage of this strategy is that the substitution can be chosen at a late stage of the synthesis. Differently substituted CPPs were thus synthesized. Structural properties of the substituted CPPs are similar to those of unsubstituted CPPs, with small variations in optical properties. Future work will examine the special properties of substituted CPPs, the synthetic strategy toward longer fragments of carbon nanotubes, and applications in nanoporous materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthesis and characterization of all new compounds; crystallographic data of **7a**, **8b**, and **9d**; details of theoretical modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Hermann.A.Wegner@org.Chemie.uni-giessen.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the University of Basel, Staatssekreteriat für Bildung und Forschung SBF, COST MP0901 NanoTP, and French ANR-2010-BLAN-0819-04 "SPRINT".

■ REFERENCES

(1) Tahara, K.; Tobe, Y. *Chem. Rev.* **2006**, *106*, 5274.

(2) Omachi, H.; Nakayama, T.; Takahashi, E.; Segawa, Y.; Itami, K. *Nat. Chem.* **2013**, *5*, 572.

(3) Jasti, R.; Bhattacharjee, J.; Neaton, J. B.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 17646.

(4) (a) Xia, J.; Jasti, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 2474. (b) Xia, J.; Bacon, J. W.; Jasti, R. *Chem. Sci.* **2012**, *3*, 3018. (c) Sisto, T. J.; Jasti, R. *Synlett* **2012**, *23*, 483. (d) Omachi, H.; Segawa, Y.; Itami, K. *Acc. Chem. Res.* **2012**, *45*, 1378. (e) Kayahara, E.; Sakamoto, Y.; Suzuki, T.; Yamago, S. *Org. Lett.* **2012**, *14*, 3284. (f) Ishii, Y.; Nakanishi, Y.; Omachi, H.; Matsuura, S.; Matsui, K.; Shinohara, H.; Segawa, Y.; Itami, K. *Chem. Sci.* **2012**, *3*, 2340. (g) Darzi, E. R.; Sisto, T. J.; Jasti, R. *J. Org. Chem.* **2012**, *77*, 6624. (h) Sisto, T. J.; Golder, M. R.; Hirst, E. S.; Jasti, R. *J. Am. Chem. Soc.* **2011**, *133*, 15800. (i) Segawa, Y.; Šenel, P.; Matsuura, S.; Omachi, H.; Itami, K. *Chem. Lett.* **2011**, *40*, 423. (j) Segawa, Y.; Miyamoto, S.; Omachi, H.; Matsuura, S.; Šenel, P.; Sasamori, T.; Tokitoh, N.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3244. (k) Iwamoto, T.; Watanabe, Y.; Sakamoto, Y.; Suzuki, T.; Yamago, S. *J. Am. Chem. Soc.* **2011**, *133*, 8354. (l) Yamago, S.; Watanabe, Y.; Iwamoto, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 757. (m) Omachi, H.; Matsuura, S.; Segawa, Y.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 10202. (n) Jasti, R.; Bertozzi, C. R. *Chem. Phys. Lett.* **2010**, *494*, 1. (o) Takaba, H.; Omachi, H.; Yamamoto, Y.; Bouffard, J.; Itami, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6112. (p) Evans, P. E.; Darzi, E. R.; Jasti, R. *Nat. Chem.*, in press. (q) Kayahara, E.; Patel, V. K.; Yamago, S. *J. Am. Chem. Soc.* **2014**, *136*, 2284.

(5) (a) Zabula, A. V.; Filatov, A. S.; Xia, J.; Jasti, R.; Petrukhina, M. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 5033. (b) Fomine, S.; Zolotukhin, M.; Guadarrama, P. *J. Mol. Model.* **2012**, *18*, 4025. (c) Iwamoto, T.; Watanabe, Y.; Sadahiro, T.; Haino, T.; Yamago, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 8342.

(6) (a) Camacho, C.; Niehaus, T. A.; Itami, K.; Irle, S. *Chem. Sci.* **2013**, *4*, 187. (b) Segawa, Y.; Fukazawa, A.; Matsuura, S.; Omachi, H.; Yamaguchi, S.; Irle, S.; Itami, K. *Org. Biomol. Chem.* **2012**, *10*, 5979. (c) Nishihara, T.; Segawa, Y.; Itami, K.; Kanemitsu, Y. *J. Phys. Chem. Lett.* **2012**, *3*, 3125. (d) Li, H.-B.; Page, A. J.; Irle, S.; Morokuma, K. *ChemPhysChem* **2012**, *13*, 1479. (e) Fujitsuka, M.; Cho, D. W.; Iwamoto, T.; Yamago, S.; Majima, T. *Phys. Chem. Chem. Phys.* **2012**, *14*, 14585. (f) Sundholm, D.; Taubert, S.; Pichierri, F. *Phys. Chem. Chem. Phys.* **2010**, *12*, 2751. (g) Segawa, Y.; Omachi, H.; Itami, K. *Org. Lett.* **2010**, *12*, 2262. (h) Bachrach, S. M.; Stück, D. *J. Org. Chem.* **2010**, *75*, 6595. (i) Wong, B. M. *J. Phys. Chem. C* **2009**, *113*, 21921.

(7) (a) Yagi, A.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 2962. (b) Sisto, T. J.; Tian, X.; Jasti, R. *J. Org. Chem.* **2012**, *77*, 5857. (c) Nishiuchi, T.; Feng, X.; Enkelmann, V.; Wagner, M.; Müllen, K. *Chem.—Eur. J.* **2012**, *18*, 16621.

(8) (a) O'Mahony, A. M.; Wang, J. *Analytical Methods* **2013**, *5*, 4296. (b) Miles, B. N.; Ivanov, A. P.; Wilson, K. A.; Doğan, F.; Japrung, D.; Edel, J. B. *Chem. Soc. Rev.* **2013**, *42*, 15.

(9) Bharat; Bhola, R.; Bally, T.; Valente, A.; Cyrański, M. K.; Dobrzycki, Ł.; Spain, S. M.; Rempała, P.; Chin, M. R.; King, B. T. *Angew. Chem., Int. Ed.* **2010**, *49*, 399.

(10) Friederich, R.; Nieger, M.; Vögtle, F. *Chem. Ber.* **1993**, *126*, 1723.

(11) Srinivasan, M.; Sankararaman, S.; Hopf, H.; Varghese, B. *Eur. J. Org. Chem.* **2003**, *2003*, 660.

(12) Höger, S.; Bonrad, K. *J. Org. Chem.* **2000**, *65*, 2243.