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Synthesis of Molecular Nanocages by Click Chemistry

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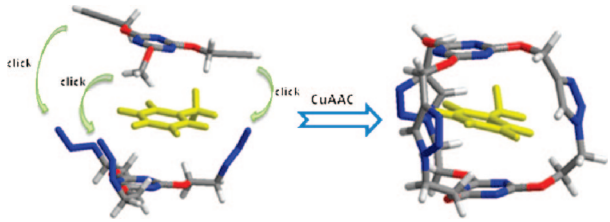

The covalent synthesis of nanosized cage compounds is easily performed in high yields using "click chemistry" methodology through the Cu(I)-catalyzed ligation of adequate polyalkyne and polyazide derivatives using $(EtO)_3P\cdot CuI$ as catalyst.

Cage-type molecules[1] have attracted considerable research interest from supramolecular chemists[2] considering their capability to act as molecular host, which can be exploited in applications such as storage,[3] recognition,[4] delivery, [5] and catalysis.[6] These molecular cages are unique as they normally have finite and structurally well-defined intramolecular cavities that can interact with either a cationic, anionic, or neutral guest through noncovalent interactions providing size- and shape-dependent selectivity in addition to an insight into the molecular recognition phenomena in a confined space that is prevalent in nature.

The synthesis of three-dimensional shape-persistent molecules is usually laborious, and different approaches have been developed.[1b] These molecular containers can be made as single, large covalently joined molecules but also as self-assembled supramolecular constructs using noncovalent interactions. In this last approach, the use of metal-directed assembling techniques[7] provides a great deal of versatility in the construction of complex geometries, while the formation of capsules via noncovalent assembling[8] of molecules allows a templated assembly in solution around the guests. Up to the present, most efforts have been directed toward the construction of self-assembled supramolecular cages having large cavities, and the efficient covalent synthesis of nanosized cage compounds with high symmetry still remains a challenge.

In this context, copper(I)-catalyzed azido-alkyne cycloaddition (CuAAC),[9] nowadays the best reaction under the "click chemistry" concept,[10] appears as an appealing synthetic tool for the construction of molecular nanocages considering its efficiency, which has been validated by the numerous applications that this reaction has found in almost all areas of chemistry (drug discovery,[11] bioconjugation,[12] polymer and science materials,[13] and related areas [14]) including supramolecular chemistry.[15] Continuing our efforts in the applications of click chemistry in the construction of multivalent structures[16] and materials[17] with a well-defined architecture, we reported in the preceeding contribution of this issue the successful implementa-

(1) (a) *Container Molecules and Their Guests*; Cram, D. J., Cram, J. M., Eds.; Royal Society of Chemistry: Cambridge, U.K.,1997. (b) Turner, D. R.; Pastor, A.; Alajarin, M.; Steed, J. W. In *Supramolecular Assembly via Hydrogen Bonds I*; Springer: Berlin, 2004; Vol. 108, pp 97−168. (c) Jeppesen, J. O.; Nielsen, M. B.; Becher, J. *Chem. Rev.* **2004**, *104*, 5115. (d) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931.

(2) (a) *Comprehensive Supramolecular Chemistry*; Lehn, J. M., Atwood, J. L., Davies, J. E. D., McNicol, D. D., Vogtle, F., Eds.; Pergamon, Elsevier Science: Oxford, 1996. (b) *Encyclopedia of Supramolecular Chemistry*; Atwood, J. L., Steed, J. W., Eds.; Marcel Dekker: New York, 2004.

(3) (a) Martin, T.; Obst, U.; Rebek, J., Jr. *Science* **1998**, *281*, 1842. (b) Davis, A. V.; Raymond, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 7912. (c) Kusukawa, T.; Fujita, M. *J. Am. Chem. Soc.* **2002**, *124*, 13576.

(4) (a) Heinz, T.; Rudkevich, D. M.; Rebek, J., Jr. *Nature* **1998**, *394*, 764. (b) Tashiro, S.; Tominaga, M.; Kawano, M.; Therrien, B.; Ozki, T.; Fujita, M. *J. Am. Chem. Soc.* **2005**, *127*, 4546. (c) Kerchoffs, J. M. C. A.; van Leeuwen, F. W. B.; Spek, A. L.; Kooijman, H.; Crego-Calama, M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5717.

(5) (a) Turner, J. L.; Wooley, K. L. *Nano Lett.* **2004**, *4*, 683. (b) Pan, D.; Turner, J. L.; Wooley, K. L. *Chem. Commun.* **2003**, 2400. (c) Perkin, K. K.; Turner, J. L.; Wooley, K. L.; Mann, S. *Nano Lett.* **2005**, *5*, 1457.

(6) (a) Fiedler, D.; Leung, D. H.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2005**, *38*, 351. (b) Yoshizawa, M.; Takeyama, Y.; Kusukawa, T.; Fujita, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1347.

(7) (a) Jacopozzi, P.; Dalcanale, E. *Angew. Chem., Int. Ed. Engl.* **1997**, 36. (b) Fujita, M. *Chem. Soc. Rev.* **1998**, *27*, 417. (c) Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem. Rev.* **2000**, *100*, 853–907. (d) Swiegers, G. F.; Malefetse, T. J. *Chem. Rev.* **2000**, *100*, 3483. (e) Warmuth, R.; Yoon, J. *Acc. Chem. Res.* **2001**, *34*, 95.

(8) (a) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488. (b) Lutzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1000. (c) Johnston, M. R.; Latter, M. J. *Supramol. Chem.* **2005**, *17*, 595. (d) Rebek, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2068. (e) Schmuck, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5830.

(9) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(10) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2005.

(11) (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (b) Roper, S.; Kolb, H. C. *Fragment-Based Approaches in Drug Discovery*; Wiley-VCH: Weinheim, 2006; Methods and Principles in Medicinal Chemistry Vol. 34, p 313. (c) Sharpless, K. B.; Manetsch, R. *Expert Opin. Drug Discovery* **2006**, *1*, 525. (d) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278.

(12) (a) Pieters, R. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *QSAR Comb. Sci* **2007**, *26*, 1181. (b) Dirks, A. J.; Cornelissen, J.; van Delft, F. L.; van Hest, J. C. M.; Nolte, R. J. M.; Rowan, A. E.; Rutjes, F. *QSAR Comb. Sci.* **2007**, *26*, 1200. (c) Salisbury, C. M.; Cravatt, B. F. *QSAR Comb. Sci.* **2007**, *26*, 1229. (d) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674. (e) Baskin, J. M.; Bertozzi, C. R. *QSAR Comb. Sci.* **2007**, *26*, 1211. (f) Lutz, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2182. (g) Lutz, J. F.; Borner, H. G. *Prog. Polym. Sci.* **2008**, *33*, 1.

(13) (a) Binder, W. H.; Kluger, C. *Curr. Org. Chem.* **2006**, *10*, 1791. (b) Nandivada, H.; Jiang, X. W.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197. (c) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* **2007**, *28*, 15. (d) Lutz, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018. (e) Fournier, D.; Hoogenboom, R.; Schubert, U. S. *Chem. Soc. Rev.* **2007**, *36*, 1369. (f) Golas, P. L.; Matyjaszewski, K. *QSAR Comb. Sci.* **2007**, *26*, 1116. (g) Devaraj, N. K.; Collman, J. P. *QSAR Comb. Sci.* **2007**, *26*, 1253.

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tion of CuAAC in the synthesis of calixarene-based cavitands and nanotubes.[18] In the majority of the syntheses in which CuAAC has found applications, the reactions are conducted between monofunctional building blocks (monoalkynes and monoazides) or between a polyfunctional substrate (polyalkynes or polyazides) and a monofuncional complementary counterpart (monoazides or monoalkynes, respectively). However, the reported cases in which polyalkynes and polyazides have been reacted are less abundant, having found application mainly in the synthesis of polymers[13] by means of intermolecular ligation process. Our click synthesis of discrete calixarene-based molecular receptors evidenced[18] that CuAAC of dialkyne and diazide calixarene derivatives led exclusively to the formation of cyclic compounds (cyclomonomers and cyclodimers) through molecular connections formed by an inter-intramolecular tandem process, the formation of the corresponding polymerization compounds not being observed.

Taking into account these results, it was thought that click chemistry should also allow the easy construction of three-dimensional shape-persistent molecular nanocages containing multiple connecting triazole spanners by the reaction of complementary polyalkynes and polyazides with an equal degree of multivalency higher than two (Figure 1). Such compounds bearing more than two identical clickable functions have been previously used mainly in the reaction with other multivalent counterparts with a different degree of multivalency for the construction of nonlinear molecular architectures such as gel and polymer networks in which the click chemistry plays the role of a highly efficient cross-linking reaction.[13] This strategy has been applied to small clickable molecules acting as monomers and also to some homofunctional clickable telechelic polymers acting as macromonomers that are cross-linked through their end groups with complementary multifunctional small molecules. However, to the best of our knowledge,

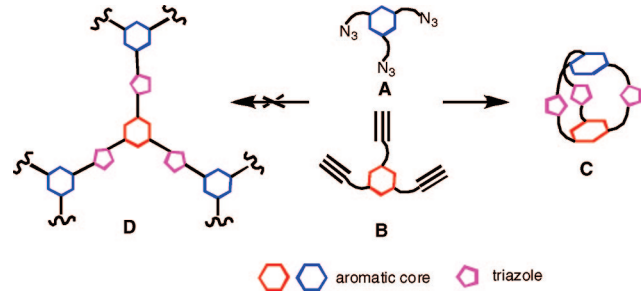
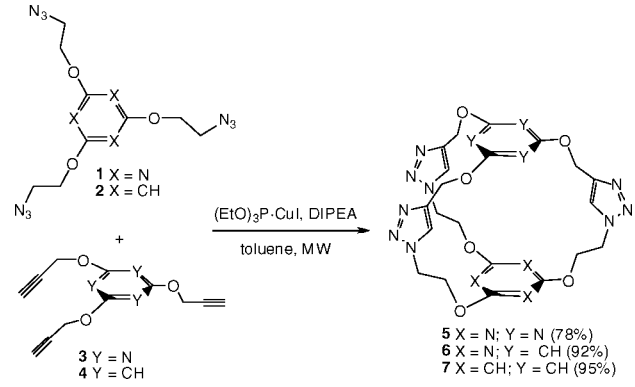


FIGURE 1. Different possible pathways in the CuACC of triazides with trialkynes.

SCHEME 1. Synthesis of Molecular Cages



CuAAC of a pair of complementary homofunctionalized click compounds with an equal degree of multivalency has been only smartly used by Finn et al.[19] to generate a cross-linked polymer network with applications as an adhesive coating to glue copper plates together by means of the noncovalent interactions exerted by the acetylenes and formed triazoles. In order to construct nanocages (structure C, Figure 1), the click intramolecular ligation of polyalkynes and polyazides should be favored after the first click over the intermolecular reactions that lead to polymers (structure D, Figure 1). It was hypothesized that this could be achieved by using polyvalent alkynes and azides derived from aromatic molecules when performing the reactions under high dilution conditions in an aromatic solvent such as toluene that should enable a template effect by means of π-stacking interactions. The cofacial π-stacking of aromatic compounds is a fundamental noncovalent interaction that has long been recognized as a central feature in nature and used on a synthetic level in materials science, synthesis, molecular recognition, and supramolecular chemistry.[20]

For the implementation of our hypothesis, the trivalent triazine and benzene derivatives **1**−**4** were selected considering their easy preparation from the corresponding commercial precursors and also their rigidity. To our delight it was found that the reactions of the triazides **1**[16b] and **2**[21] with the complementary

(14) (a) Zhou, Z.; Fahrni, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 8862. (b) Link, A. J.; Vink, M. K. S.; Tirrell, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 10598. (c) Lewis, W. G.; Magallon, F. G.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2004**, *126*, 9152. (d) Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, *6*, 4603. (e) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2005**, 51. (f) Wu, P.; Fokin, V. V. *Aldrichimica Acta* **2007**, *40*, 7. (g) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (h) Kalesh, K. A.; Yang, P. Y.; Srinivasan, R.; Yao, S. Q. *QSAR Comb. Sci.* **2007**, *26*, 1135. (i) Santoyo-Gonzalez, F.; Hernandez-Mateo, F. *Top. Heterocycl. Chem.* **2007**, *7*, 133. (j) Lutz, J.-F.; Schlaad, H. *Polymer* **2008**, *49*, 817.

(15) For selected reviews, see: (a) Miljanic, O. S.; Dichtel, W. R.; Aprahamian, I.; Rohde, R. D.; Agnew, H. D.; Heath, J. R.; Stoddart, J. F. *QSAR Comb. Science* **2007**, *26*, 1165. (b) Aprahamian, I.; Miljanic, O. S.; Dichtel, W. R.; Isoda, K.; Yasuda, T.; Kato, T.; Stoddart, J. F. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1856. (c) Braunschweig, A. B.; Dichtel, W. R.; Miljanic, O. S.; Olson, M. A.; Spruell, J. M.; Khan, S. I.; Heath, J. R.; Stoddart, J. F. *Chem. Asian J.* **2007**, *2*, 634. For selected papers see: (d) Aucagne, V.; Haenni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 2186. (e) O'Reilly, R. K.; Joralemon, M. J.; Hawker, C. J.; Wooley, K. L. *Polym. Sci. Polym. Chem.* **2006**, *44*, 5203. (f) Diaz, D. D.; Rajagopal, K.; Strable, E.; Schneider, J.; Finn, M. G. *J. Am. Chem. Soc.* **2006**, *128*, 6056. (g) Gil, M. V.; Arevalo, M. J.; Lopez, O. *Synthesis* **2007**, 1589. (h) Zhang, W. B.; Tu, Y.; Ranjan, R.; VanHorn, R. M.; Leng, S.; Wang, J.; Polce, M. J.; Wesdemiotis, C.; Quirk, R. P.; Newkome, G. R.; Cheng, S. Z. D. *Macromol.* **2008**, *41*, 515. (i) Marois, J. S.; Cantin, K.; Desmarais, A.; Morin, J. F. *Org. Lett.* **2008**, *10*, 33.

(16) (a) Calvo-Flores, F. G.; Isac-García, J.; Hernandez-Mateo, F.; Perez-Balderas, F.; Calvo-Asín, J. A.; Sanchez-Vaquero, E.; Santoyo-González, F. *Org. Lett.* **2000**, *2*, 2499. (b) Perez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernandez-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asin, J. A.; Isac-Garcia, J.; Santoyo-Gonzalez, F. *Org. Lett.* **2003**, *5*, 1951. (c) Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Perez-Balderas, F.; Hernandez-Mateo, F.; Giron-Gonzalez, M. D.; Sevillano-Tripero, N.; Salto-Gonzalez, R.; Santoyo-Gonzalez, F. *Org. Biomol. Chem.* **2007**, *5*, 2291.

(17) Ortega-Muñoz, M.; Lopez-Jaramillo, J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Adv. Synth. Catal.* **2006**, *348*, 2410.

(18) Morales-Sanfrutos, J.; Ortega-Mũnoz, M.; Lopez-Jaramillo, J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *J. Org. Chem.* **2008**, *73*, 7768.

(19) Diaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4392.

(20) (a) Fyfe, M. C. T.; Stoddart, J. F. *Acc. Chem. Res.* **1997**, *30*, 393. (b) Adams, H.; Hunter, C. A.; Lawson, K. R.; Perkins, J.; Spey, S. E.; Urch, C. J.; Sanderson, J. M. *Chem. Eur. J.* **2001**, *7*, 4863. (c) Pease, A. R.; Jeppesen, J. O.; Stoddart, J. F.; Luo, Y.; Collier, C. P.; Heath, J. R. *Acc. Chem. Res.* **2001**, *34*, 433. (d) Klarner, F.-G.; Kahlert, B. *Acc. Chem. Res.* **2003**, *36*, 919. (e) Harmata, M. *Acc. Chem. Res.* **2004**, *37*, 862.

(21) Grigoryan, S. G.; Avetisyan, K. G.; Arzumanyan, A. M.; Mardoyan, M. K.; Matnishyan, A. A. *Khim. Promst., Ser.: Reak. Osobo Chist. Veshchestva* **1981**, *32*, CAN96:85520.

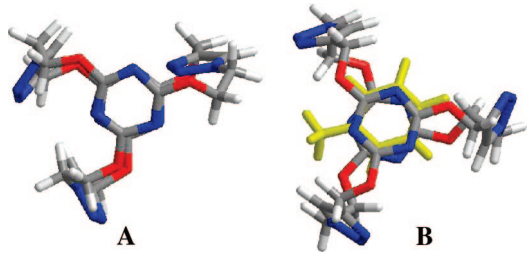


FIGURE 2. Calculated structures for hollow nanocage **5** (A) and for the host−guest 5-toluene complex (B).

functionalized trialkynes **3** and **4**[22] using toluene as solvent and microwave irradiation led to the molecular nanocages **5**−**7** in high yields (see Scheme 1). In order to assess the feasibility of the coupling reactions when microwave irradiation is not used, the coupling reaction of **1** and **3** was also performed using refluxing toluene, and it was observed that slightly higher reaction times (5 h versus 4 h) are required, the nanocage **5** being isolated in slightly lower yields (66% versus 78%). However, the reactions were unproductive when DMF was used as solvent, and in addition, the ^{1}H NMR spectra of such compounds (when registered at 80 °C using DMSO-d_6 as solvent) indicated the presence of an encapsulated molecule of toluene in the cavity of those cages that could be only removed by a successive freeze-drying process of the solid materials using DMSO−H_2O (1:1) as solvent. Both results reinforce our hypothesis about the template effect played by toluene. These cage compounds are highly insoluble solids at room temperature in a wide variety of solvents (chloroform, dichloromethane, ethyl acetate, dimethylformamide, pyridine, DMSO). The MS data (FAB+) are in agreement with the proposed structures.

All of the cage-type molecules exhibited symmetric structures in solution, as judged from their simple NMR spectra and from the molecular modeling studies performed for **5** to assess the feasibility of toluene being inside the boxes (Figure 2). Geometrical minimization by molecular mechanics converged at the same magnitude of energy with an improvement of 2 and 9 orders of magnitude for the hollow cages and the cage hosting toluene, respectively. Further minimization with a semiempirical quantum mechanism led to structures where the toluene is placed inside the cage with the methyl group pointing to the open side. The facts that the cage hosting toluene shows lower energy than the hollow one and that the toluene is arranged between the six-membered aromatic rings are compatible with a stabilizing π-stacking.

The ensemble of the reported results herein about the easy synthesis of molecular containers by CuAAC are indicative of the high steric tolerance of the click chemistry, which is in accordance with previously reported[23] preparations of other high sterically demanding structures.

In summary, we have implemented the click chemistry concept in the synthesis of molecular cages by the chemical ligation of adequate polyazides and polyalkyne derivatives using the organic soluble copper(I) complex $(EtO)_3P\cdot CuI$. The high yields and exclusive formation of these compounds highlight the efficiency of the approach.The synthetic strategy offers a facile and highly convergent methodology extensible for the modular preparation of supramolecular entities of diverse architectures.

Experimental Section

Synthesis of Nanocage 5. Method A. A solution of triazide **1** (168 mg, 0.5 mmol), trialkyne derivative **3** (122 mg, 0.5 mmol), DIPEA (797 μL, 4.46 mmol), and the copper catalyst [$(EtO)_3P\cdot CuI$] (27 mg, 0.073 mmol) in toluene (75 mL) was irradiated at 800 W and 100 °C (4 h) in a Microwave Labstation until thin layer chromatography and the IR spectra of the reaction mixture showed complete disappearance of the starting materials (4 h). The resulting solid was filtered and washed successively with toluene and dried under vacuum at 50 °C, yielding **5** (226 mg, 78%): mp > 255 °C (dec); IR (KBr) 1561, 1415, 1329, 1127 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.31 (br s, 3 H), 5.47 (br s, 6 H), 4.78 (Br s, 12 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 172.2, 172.1, 141.5, 125.6, 78.4, 67.0, 55.6, 48.3; HRMS (FAB+) *m*/*z* calcd for $C_{21}H_{21}N_{15}O_6$ 579.1799, found 579.1798.

Method B. Reaction of **1** and **3** under refluxing toluene (75 mL) for 5 h in the presence of DIPEA as base and $(EtO)_3P\cdot CuI$ as the copper catalyst, using similar amounts of all reagents as those described above for Method A, yields a solid that after filtering, washing with toluene, and drying under vacuum at 50 °C was characterized as compound **5** (191 mg, 66%).

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Supporting Information Available: Instrumentation, general experimental methods, experimental procedures for preparation and compound characterization data of **2** and **5**−**7**, as well as copies of ^{1}H NMR, ^{13}C NMR and MS spectra for compounds **2** and **6**−**7** and Cartesian coordinates for **5** and **5**-toluene host−guest complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Berscheid, R.; Nieger, M.; Voegtle, F. *J. Chem. Soc., Chem. Commun.* **1991**, 1364.

(23) Helms, B.; Mynar, J. L.; Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15020.