ORGANIC LETTERS

2006
Vol. 8, No. 26
5991−5994

# Regioselectively *N*-Methylated Azacalix[8]arene Octamethyl Ether Prepared by Catalytic Aryl Amination Reaction Using a Temporal *N*-Silylation Protocol

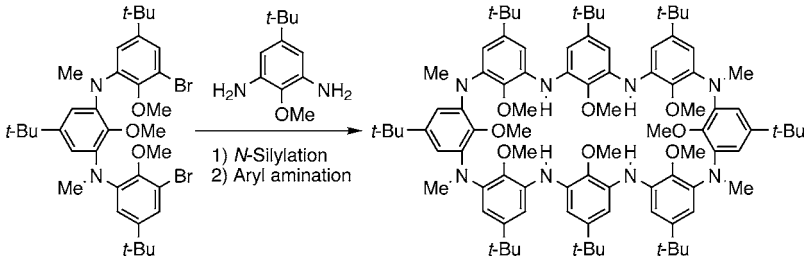
**Koichi Ishibashi, Hirohito Tsue,* Satoshi Tokita, Kazuhiro Matsui, Hiroki Takahashi, and Rui Tamura**

*Graduate School of Human and Environmental Studies, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan*

*tsue@ger.mbox.media.kyoto-u.ac.jp*

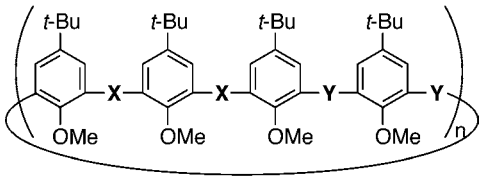
**Received October 6, 2006**

## ABSTRACT




**A temporal *N*-silylation protocol in the catalytic aryl amination reaction has been devised to prepare nitrogen-bridged calixarene analogues. The protocol involves a smooth in situ *N*-silylation before aryl amination reaction, followed by spontaneous cleavage of the N–Si bond in the usual workup process, to furnish secondary aromatic amines as the cross-coupled product with no silyl group on the nitrogen atom. A successful application to the preparation of regioselectively *N*-methylated azacalix[8]arene is described, together with the crystallographic analysis.**

Heteroatom-bridged calixarenes, in which methylene bridges are replaced by heteroatoms, have attracted much interest as a new class of calixarene scaffolds because of the intriguing properties distinct from those of the "original" calixarenes.[1,2] For the preparation of heteroatom-bridged calixarenes, three typical synthetic strategies have so far been employed that are substantially identical with those established in the methylene-bridged calixarene chemistry:[3,4] that is, (1) single-step synthesis, (2) non-convergent stepwise synthesis, and (3) convergent fragment coupling synthesis.[3] From a synthetic point of view, strategy 1 is undoubtedly favorable, whereas the latter two alternatives may provide a more versatile and flexible synthetic approach, by which boron-,[5] germanium-,[6] nitrogen-,[7] oxygen-,[8] silicon-,[9] phosphorus-,[9b] and sulfur-bridged[10] calixarene analogues were synthesized.




**1**: **X** = **Y** = NMe, n = 1
**2**: **X** = NMe, **Y** = NBn, n = 1
**3**: **X** = NMe, **Y** = NH, n = 2
**4**: **X** = NMe, **Y** = NH, n = 1
**5**: **X** = **Y** = $CH_2$, n = 2

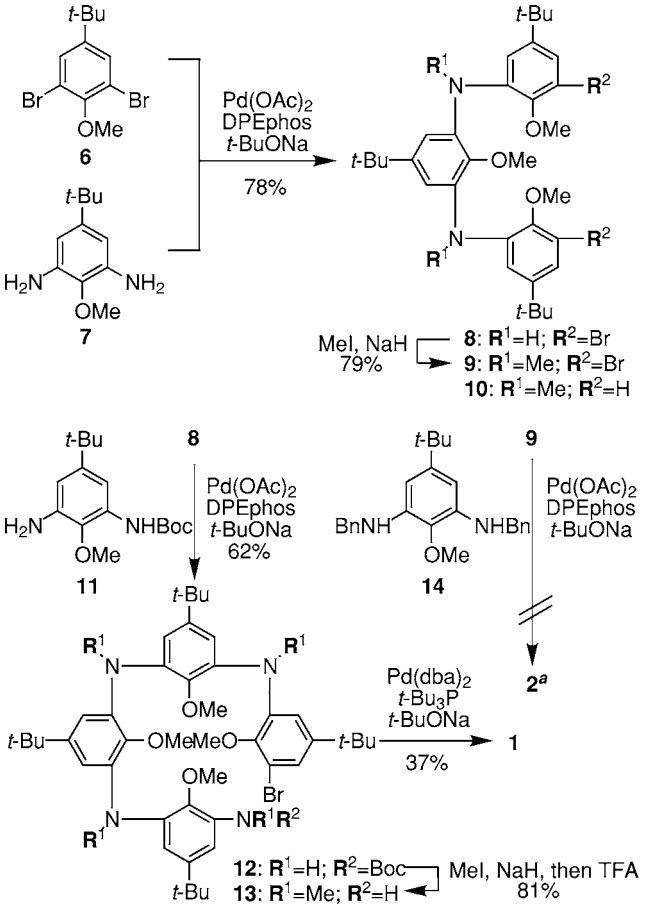
(1) *Calixarenes 2001*; Asfari, Z., Böhhmer, V., Harrowfield, J., Vicens, J., Saadioui, M., Eds.; Kluwer: Dordrecht, The Netherlands, 2001.

(2) For a review on heteroatom-bridged calixarenes: König, B.; Fonseca, M. H. *Eur. J. Inorg. Chem.* **2000**, 2303.

10.1021/ol062459p CCC: $33.50 
**Published on Web 11/22/2006**

In the course of our study aiming at developing a novel host molecule, we very recently reported the preparation of exhaustively methylated azacalix[4]arene **1**[7k] by applying strategy 2 shown in Scheme 1, where Buchwald−Hartwig

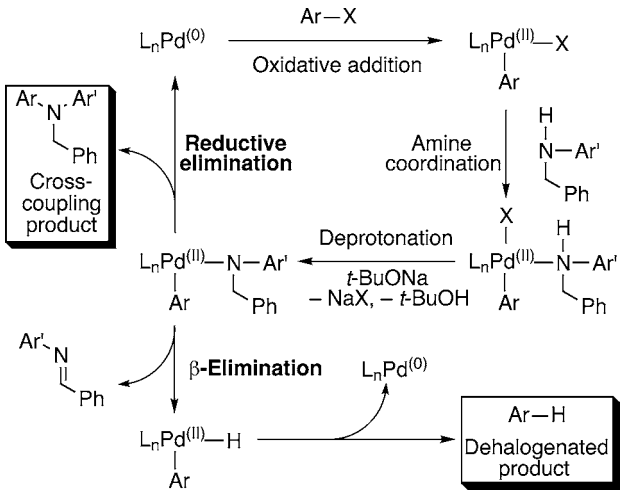
**Scheme 1.** Synthesis of Azacalix[4]arene **1** by No Application of the Temporal *N*-Silylation Protocol




[a] Debrominated trimer **10** was obtained in 56% yield.

aryl amination reaction[11] was repeatedly utilized for the synthesis of **1** starting from monomers **6** and **7** via intermediate linear oligomers **8**, **12**, and **13**. As a natural consequence, our efforts were directed to the establishment of a "shortcut" by the usage of strategy 3, in which the palladium-catalyzed aryl amination reaction was applied to the direct coupling between trimer **9** and monomer **14**.[12] Benzyl groups, easily cleavable by hydrogenolysis in due course, were introduced onto the amino groups of **14**. However, the corresponding azacalix[4]arene **2** and other possible cyclized products were not isolated from the reaction mixture. Instead, debrominated trimer **10** was obtained in 56% yield, clearly indicating that the competitive $\beta$-elimination pathway giving **10** proceeded in preference to desirable reductive elimination yielding **2**, as shown in Scheme 2.[11a,13]

**Scheme 2.** Catalytic Cycle of the Buchwald−Hartwig Aryl Amination Reaction of Aromatic Halide with *N*-Benzylated Arylamine[11a]




To suppress the undesirable $\beta$-elimination in the catalytic cycle, efficient ligands such as *t*-Bu$_3$P, DPEphos,[14] Xantphos,[15] and Johnphos[16] were devised.[17] In the present study,

(3) (a) Gutsche, C. D. *Calixarenes*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, UK, 1989. (b) Gutsche, C. D. *Calixarenes Revisited*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, UK, 1998.

(4) *Calixarenes*: *A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, J. V., Eds.; Kluwer: Dordrecht, The Netherlands, 1991.

(5) Carré, F. H.; Corriu, R. J.-P.; Deforth, T.; Douglas, W. E.; Siebert, W. S.; Weinmann, W. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 652.

(6) König, B.; Rödel, M. *Chem. Ber.* **1997**, *130*, 412.

(7) (a) Graubaum, H.; Lutze, G.; Costisella, B. *J. Prakt. Chem./Chem.-Ztg.* **1997**, *339*, 266. (b) Graubaum, H.; Lutze, G.; Costisella, B. *J. Prakt. Chem./Chem.-Ztg.* **1997**, *339*, 672. (c) Ito, A.; Ono, Y.; Tanaka, K. *New J. Chem.* **1998**, 779. (d) Ito, K.; Ono, Y.; Tanaka, K. *J. Org. Chem.* **1999**, *64*, 8236. (e) Ito, K.; Ono, Y.; Tanaka, K. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1072. (f) Miyazaki, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2002**, *43*, 7945. (g) Wang, M.-X.; Zhang, X.-H.; Zheng, Q.-Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 838. (h) Wang, M.-X.; Yang, H.-B. *J. Am. Chem. Soc.* **2004**, *126*, 15412. (i) Suzuki, Y.; Yanagi, T.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, 263. (j) Fukushima, W.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, 2931. (k) Tsue, H.; Ishibashi, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2005**, *7*, 2165. (l) Yan, X. Z.; Pawlas, J.; Goodson, T., III; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 9105.

(8) (a) Sommer, N.; Staab, H. A. *Tetrahedron Lett.* **1966**, *25*, 2837. (b) Katz, J. L.; Feldman, B.; Conry, R. R. *Org. Lett.* **2005**, *7*, 91.

(9) (a) König, B.; Rödel, M.; Bubenitschek, P.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 661. (b) König, B.; Rödel, M.; Bubenitschek, P.; Jones, P. G.; Thondorf, J. *J. Org. Chem.* **1995**, *60*, 7406.

(10) (a) Nakayama, J.; Katano, N.; Suhihara, Y.; Ishii, A. *Chem. Lett.* **1997**, 897. (b) Sone, T.; Ohba, K.; Moriya, K.; Kumada, H.; Ito, K. *Tetrahedron* **2000**, *53*, 10689.

(11) For reviews on the palladium-catalyzed aryl amination reaction: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (d) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 133.

(12) As reported in ref 7k, a simpler cyclization of **7** with **8** afforded a complicated reaction mixture.

(13) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626.

(14) DPEphos: bis[2-(diphenylphosphino)phenyl] ether. Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081.

(15) Xantphos: 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene. See ref 14 for the preparation.

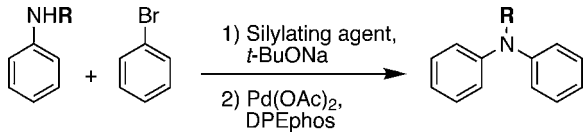
(16) Johnphos: 2-(di-*tert*-butylphosphino)biphenyl. Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

(17) For a review on phosphine ligands: Mauger, C. C.; Mihnani, G. A. *Aldrichim. Acta* **2006**, *39*, 17.

we examined an additional procedure in which the silyl group without any hydrogen on the silicon atom was attached onto an amino group in place of methyl and benzyl groups hitherto used in our synthetic pathways. As an eventual outcome, we found this method highly efficient for the palladium-catalyzed aryl amination reaction in terms of the following three points. First, *N*-silylation of the amino group smoothly proceeds in situ. Second, the resultant silylamine is subjected in one pot to the cross-coupling reaction with aromatic halide. Third and finally, the *N*-silylation of the amino group is temporal because the N−Si bond is labile to hydrolysis,[18] thereby furnishing the final cross-coupling product with no silyl group on the nitrogen atom after the usual workup process. In this paper, we report a temporal *N*-silylation protocol in the catalytic aryl amination reaction and a successful application of it to the preparation of regioselectively *N*-methylated azacalix[8]arene octamethyl ether **3**.

As a model reaction, the aryl amination reaction of aniline with bromobenzene was examined to establish the general procedure of the temporal *N*-silylation protocol. Essentially the same reaction conditions as those employed in the cross-coupling reaction **6** + **7** → **8**[7k] were applied to this model reaction. A control experiment was conducted with *N*-benzylaniline, which was transformed to the corresponding cross-coupling product in 38% yield (entry 1 in Table 1). In contrast, the reaction yield was drastically improved to 79% in entry 2, where an equimolar amount of dimethylphenylsilyl chloride (DMPSCl) was employed. Unlike entry 1, the DMPS group introduced in situ onto the nitrogen atom was deprotected after the usual workup because of the high instability of N−Si bond to water[18] used in the extraction process, thus allowing the temporal protection of the amino group only during the reaction. A similar result was obtained for *tert*-butyldiphenylsilyl chloride (TBDPSCl), whereas *tert*-butyldimethylsilyl chloride (TBDMSCl) and triphenylsilyl chloride (TPSCl) failed to give good yields. The exact reason for the observed variation in the reaction yields by the use of different silylating agents remains unclear at this moment. Nevertheless, the DMPS group was demonstrated to be the best among the silylating agents examined herein, and thus a general procedure for the temporal *N*-silylation protocol in the catalytic aryl amination reaction was established.[19,20]

**Table 1.** Palladium-Catalyzed Aryl Amination Reaction of Aniline with Bromobenzene by Using the Temporal *N*-Silylation Protocol[a]




| entry | R | silylating agent | yield (%)[b] |
|---|---|---|---|
| 1 | Bn | none | 38 |
| 2 | H | DMPSCl | 79 |
| 3 | H | TBDPSCl | 70 |
| 4 | H | TBDMSCl | 36 |
| 5 | H | TPSCl | 35 |

[a] Reaction conditions of step 1: 1 mmol of aniline, 1 mmol of bromobenzene, 1 mmol of silylating agent, 3 mmol of *t*-BuONa, 2 mL of anhydrous toluene; heated at 80 °C for 30 min under an Ar atmosphere. Step 2: 5 mol % of $Pd(OAc)_2$, 7.5 mol % of DPEphos; heated at 80 °C for 18 h. [b] Yields were determined by means of normal phase HPLC analyses.

As described above, the convergent fragment coupling between trimer **9** and monomer **14** did not furnish any cyclized product. Thus, we next examined the reaction of trimer **9** with monomer **7** as an application of the temporal *N*-silylation protocol. Essentially the same reaction conditions as those employed in the final ring-closing reaction **13** → **1**[7k] in Scheme 1 were applied, and DMPSCl was used as a silylating agent. As a result, regioselectively *N*-methylated azacalix[8]arene octamethyl ether **3** was isolated in 23% yield after flash column chromatography on silica gel. However, smaller azacalix[4]arene **4** was not obtained from the reaction mixture, probably due to the highly steric demand of the DMPS group. From a thermodynamic point of view, transition state energy of the final cyclization step yielding azacalix[8]arene **3** must be lower than that of azacalix[4]arene **4** because the former must be more flexible than the latter with smaller ring size. Hence, it is reasonable to presume that kinetically favorable azacalix[8]arene **3** forms in preference to azacalix[4]arene **4** by using the temporal *N*-silylation protocol. The isolated yield of **3** (23%) was less satisfactory as a reaction but acceptable to us when considering that no cyclized products were produced in the reaction of **9** with **14**. It is worth noting that, because palladium-catalyzed cross-coupling reactions must occur four times in succession in the reaction of **9** with **7** to give **3**, the average yield of ca. 70% per one cross-coupling reaction is comparable to that observed in the model reaction mentioned above. The molecular structure of this new azacalix[8]arene **3** was fully characterized by FD MS, IR, $^1$H NMR, $^{13}$C NMR, elemental analysis, and X-ray crystallographic analysis.

A single crystal of azacalix[8]arene **3** suitable for X-ray crystallographic analysis was obtained by slow crystallization from benzene involving a few drops of acetone.[22] The compound crystallized with two molecules of benzene and half a molecule of acetone (see Figure S4 in the Supporting Information) into a monoclinic form, space group *C*2/*c* (*Z*

(18) (a) *Protective Groups in Organic Synthesis*, 3rd ed.; Green, T. W., Wuts, P. G., Eds.; Wiley & Sons: New York, 1999; p 600. (b) Fessenden, R.; Fessenden, J. S. *Chem. Rev.* **1961**, *61*, 361.

(19) General procedure (entry 2): a Schlenk tube was charged with a suspension of aniline (93.1 mg, 1.00 mmol), bromobenzene (158.4 mg, 1.01 mmol), DMPSCl (171.4 mg, 1.00 mmol), and *t*-BuONa (288.9 mg, 3.01 mmol) in anhydrous toluene (2 mL). After stirring at 80 °C for 30 min under an Ar atmosphere, $Pd(OAc)_2$ (11.9 mg, 53.0 μmol) and DPEphos (42.5 mg, 78.9 μmol) were added to the tube, and the reaction mixture was stirred at 80 °C for an additional 18 h. After cooling to room temperature, EtOAc was added. The organic layer was washed with saturated $NaHCO_3$, dried over anhydrous $K_2CO_3$, filtered, and evaporated. The resulting residue was subjected to normal phase HPLC analysis, using hexane/isopropanol (99:1, v/v) as eluent. The experimental procedure for the synthesis of azacalix[8]arene **3** is described in the Supporting Information.

(20) Applications of the temporal *N*-silylation protocol to the aromatic C−N coupling reaction are limited to the described examples at the present moment. Further studies are necessary to fully understand the scope and limitation of this newly devised protocol.

(21) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.

= 4). As shown in Figures 1 and S3, azacalix[8]arene **3** possesses a roughly ellipsoidal shape, and the conformation with $C_2$-symmetry is less symmetrical than that reported for the carbocyclic analogue **5**, which adopts a conformation with $C_{4v}$-symmetry in the solid state.[23] The asymmetric unit of **3** involves half a molecule, and the structure is described with four different types of the aromatic units designated as **A**, **B**, **C**, and **D** (Figure 1). Of them, three aromatic rings **B**, **C**, and **D** nearly lie on one plane, whereas ring **A** is considerably tilted toward the perpendicular with respect to it. Two sets of intramolecular bifurcated MeO···NH···OMe hydrogen bonds formed between rings **B** and **C** and between rings **C** and **D** are responsible for the almost flat arrangement of these three aromatic rings. In other words, aromatic ring **A** with NMe groups on both sides lacks such hydrogen bonding interactions, thereby giving rise to inclination of the ring, as observed in the 1,3-alternate conformation of our previously reported azacalix[4]arene **1**.[7k] Of further interest is the $^1$H NMR spectrum of **3** (Figure S1), the NH hydrogens of which experience a strong downfield shift at $\delta$ 6.49 ppm as compared with that of diphenylamine at $\delta$ 5.0 ppm, strongly suggesting that the intramolecular bifurcated NH···OMe hydrogen bonds are sustainable even in solution.

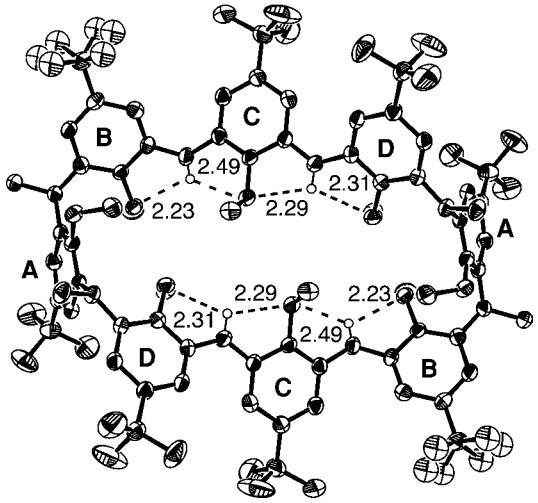



**Figure 1.** ORTEP[21] drawing of azacalix[8]arene **3**. The displacement ellipsoids are drawn at the 50% probability level. Solvent molecules and all hydrogen atoms but for the bridging NH groups are omitted for clarity. The *tert*-butyl group located on ring **B** is disordered over two positions and refined isotropically. Numbers indicate O···H distances (Å) of intramolecular MeO···NH hydrogen bonds.

In summary, we have devised a temporal *N*-silylation protocol, of which the efficiency in palladium-catalyzed aryl amination reaction has been demonstrated by the successful application to the preparation of regioselectively *N*-methylated azacalix[8]arene octamethyl ether **3**. X-ray crystallographic analysis and NMR measurement clearly revealed that intramolecular bifurcated MeO···NH···OMe hydrogen bonds between each bridging NH group and two methoxy groups located on the neighboring aromatic rings played a decisive role in the control of the conformation of **3** in the solid state and in solution. We should emphasize that the preparation of azacalix[8]arene **3** has been realized by a strategic management of stability and instability of the N−Si bond under anhydrous and moist conditions, respectively. From the present experimental results, we anticipate that the temporal *N*-silylation protocol is general and applicable to a wide variety of molecular systems. To assess our prospect, further work on the preparation of azacalix[*n*]arenes without any substituent on the bridging nitrogen atoms is currently underway in our laboratory.

**Supporting Information Available:** Experimental procedures and characterization data for all the new compounds (including NMR spectra, crystal structure, and crystallographic data in CIF format for azacalix[8]arene **3**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL062459P

(22) The X-ray data were collected on a Rigaku RAXIS RAPID imaging plate area detector. The crystal structure was solved by direct methods and refined by full-matrix least squares. All non-hydrogen atoms were refined anisotropically, except for one molecule of benzene, acetone, and disordered *tert*-butyl group that were refined isotropically. Hydrogen atoms were refined by using the riding model. All calculations were performed with a crystallographic software package, CrystalStructure version 3.7.0.[24] Crystal data for **3**·0.5 acetone·2 benzene: $M_r$ = 1659.34, monoclinic, space group *C*2/*c*, $a$ = 24.468(2) Å, $b$ = 24.214(3) Å, $c$ = 19.304(2) Å, $\beta$ = 102.267(7)°, $V$ = 11176(2) Å$^3$, $Z$ = 4, $\rho_{calc}$ = 0.986 g cm$^{-3}$, $2\theta_{max}$ = 55.0°, Mo K$\alpha$ ($\lambda$ = 0.71075 Å), $\mu$ = 0.621 cm$^{-1}$, $\theta-\omega$ scans, $T$ = 173 K, 12738 independent reflections, 11618 observed reflections, 578 refined parameters, $R1$ = 0.1226 ($I > 2\sigma(I)$), $wR2$ = 0.3856, $\Delta\rho_{max}$ = 0.89 eÅ$^{-3}$, $\Delta\rho_{min}$ = −0.31 eÅ$^{-3}$. CCDC 622392. See the Supporting Information for crystallographic data in CIF format.

(23) Bolte, M.; Brusko, V.; Böhmer, V. *J. Supramol. Chem.* **2002**, *2*, 57.

(24) *CrystalStructure*, version 3.7.0; Rigaku and Rigaku/MSC: The Woodlands, TX, 2000−2005.