Host–Guest Complexes

International Edition: DOI: 10.1002/anie.201503179
German Edition: DOI: 10.1002/ange.201503179

Synthesis and Molecular Recognition of Water-Soluble S_6-Corona[3]arene[3]pyridazines**

*Qing-Hui Guo, Liang Zhao, and Mei-Xiang Wang**

Abstract: *We report the efficient and scalable synthesis and molecular-recognition properties of novel and water-soluble S_6-corona[3]arene[3]pyridazines. The synthesis comprises a one-pot nucleophilic aromatic substitution reaction between diesters of 2,5-dimercaptoterephthalate and 3,6-dichlorotetrazine followed by the inverse electron-demand Diels–Alder reaction of the tetrazine moieties with an enamine and exhaustive saponification of esters. The resulting S_6-corona[3]arene[3]pyridazines, which adopt a 1,3,5-alternate conformation in the crystalline state, are able to selectively form stable 1:1 complexes with dicationic guest species in water with association constants ranging from $(1.10 \pm 0.06) \times 10^3\ M^{-1}$ to $(1.18 \pm 0.06) \times 10^5\ M^{-1}$. The easy availability, large cavity size, strong and selective binding power render the water-soluble S_6-corona[3]arene[3]pyridazines useful macrocyclic hosts in various disciplines of supramolecular chemistry.*

Functional macrocycles play an important role in organic and supramolecular chemistry.[1] Crown ethers,[2] cryptands,[3] spherands,[4] cyclodextrins[5] and calixarenes[6] are for instance indispensable in the study of non-covalent bond interactions, molecular recognition and self-assembly.[1,7] They also act as privileged hosts for the fabrication of sophisticated (supra)-molecular architectures and advanced materials.[8] Moreover, the tailor-made macrocycles are unique molecular tools enabling the mechanistic study of organic reactions.[9–11]

The past decade has witnessed the emergence of a few novel macrocycles. Some aesthetic molecules such as heteracalixaromatics[12] and pillararenes[13] have been shown to be versatile synthetic receptors in host–guest chemistry. Owing to the self-tunability of electronic property and V-shaped cavity originated from the interplay between the bridging heteroatoms and adjacent aromatic rings, heteracalixaromatics are able to recognize diverse guest species.[12c,d] Dichlorotetraoxacalix[2]arene[2]triazine, for example, provides a unique electron-neutral host to investigate the nascent non-covalent anion–π interactions.[14] Azacalix[1]arene[3]pyridines, on the other hand, serve as a wonderful model system for the elucidation of the mechanism of cupration because they form structurally well defined $PhCu^{II}$ and $PhCu^{III}$ organometallic compounds in copper(II)-catalyzed arene C–H bond transformations.[11]

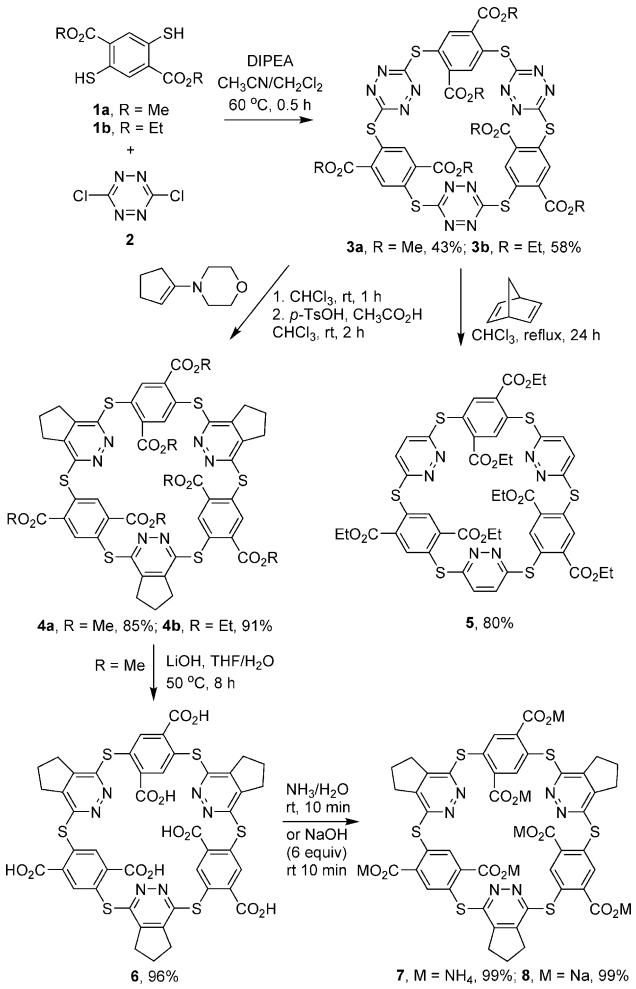
To develop macrocyclic and supramolecular chemistry, we have proposed coronarenes, a novel class of macrocycles consisting of *para*-(het)arylenes and heteroatoms in an alternate fashion.[15] Being different from 1,3-alternate heteracalixaromatics which form V-shaped clefts, coronarenes contain a cylindroid cavity. The combination of heteroatoms and (het)arenes would advantageously generate almost limitedless diverse macrocycles of regulable cavity sizes and electronic features. We report herein a highly efficient synthesis of unprecedented water-soluble S_6-corona[3]arene[3]pyridazines by one-pot nucleophilic aromatic substitution reaction (S_NAr) between diesters of 2,5-dimercaptoterephthalate and 3,6-dichlorotetrazine followed consecutively by the inverse electron-demand Diels–Alder reaction of tetrazine moieties with an enamine and complete hydrolysis of diester functionality. The resulting macrocycles acted as powerful synthetic receptors to interact selectively with electron-deficient guests in water, forming 1:1 complexes with an association constant up to $(1.18 \pm 0.06) \times 10^5\ M^{-1}$. The first S_n-corona[n]arenes ($n = 4, 5$), then were known as cyclic (*p*-phenylene sulfide)s, were obtained as by-products from polymerization of *p*-dichlorobenzene and sodium sulfide.[16] Selective synthesis of S_6-corona[6]arene, a crystalline compound of a high melting point, was later reported respectively by Franke and Vögtle[17] using *p*-bromothiophenolate and by Sergeev[18] from the reaction of a dibrominated trimer with sodium sulfide. Oxidative polymerization of diphenyl disulfide also gives S_6-corona[6]arene.[19] Except for its ring-opening polymerization to prepare linear poly(*p*-phenylene sulfide)s,[19,20] no application of S_6-corona[6]arene has been reported. S_n-corona[n]arenes containing other (het)arenes are not known.

As delineated in Scheme 1, in the presence of diisopropylethylamine (DIPEA) as an acid scavenger, dimethyl and diethyl 2,5-dimercaptoterephthalates reacted efficiently with 3,6-dichlorotetrazine at 60 °C in a mixture of acetonitrile and dichloromethane to produce S_6-corona[3]arene[3]tetrazine compounds **3a** and **3b** in 43% and 58%, respectively. Remarkably, the one-pot synthesis was readily carried out in a multi-gram scale. For example, reaction of **1b** (15 mmol) with equimolar **2** yielded 3.2 g of **3b** in 0.5 h. Treated with an electron-rich olefin derived from cyclopentanone and morpholine, the inverse electron-demand Diels–Alder reaction of tetrazine moiety led to the formation of S_6-corona[3]-arene[3]pyridazines **4a** and **4b** in high yields. A S_6-corona[3]-arene[3]pyridazine analog **5** was also synthesized in 80%

[*] Q.-H. Guo, Dr. L. Zhao, Prof. Dr. M.-X. Wang
Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education)
Department of Chemistry, Tsinghua University
Beijing 100084 (China)
E-mail: wangmx@mail.tsinghua.edu.cn

[**] We thank the National Natural Science Foundation of China (21132005, 21421064, 91427301), the Ministry of Science and Technology of China (2011CB932501), and the Tsinghua University for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201503179.



Scheme 1. Synthesis of water-soluble S_6-corona[3]arene[3]pyridazines.

yield from the inverse electron-demand Diels–Alder reaction when norbornadiene was employed instead of the enamine. Exhaustive saponification of methyl esters of **4a** using LiOH as a base yielded the acid-bearing macrocycle **6**. Transformation of acid into ammonium and sodium carboxylates furnished almost quantitatively water-soluble S_6-corona[3]arene[3]pyridazines **7** and **8**.

X-ray molecular structure reveals that both macrocycles **3b** and **6** adopt almost 1,3,5-alternate conformation in the solid state.[21] In the case of **3b**, three tetrazine rings tend to be procumbent on the same plane while three terephthalate moieties form a cone conformation (Figure 1 a and b). A more pronounced symmetric 1,3,5-alternate conformation was observed for **6** (Figure 1 c and d), with three 6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine rings in **6** being *cis*-oriented (Figure 1 d). Both macrocycles form nearly a hexagonal cavity (Figure 1 a and c). Evidenced by the bond lengths (Figure S3 in the Supporting Information), all sulfur atoms in linking positions form conjugation with electron-deficient tetrazine ring in S_6-corona[3]arene[3]tetrazine **3b**. However, both conjugation systems between sulfur linkages with pyridazine ring and terephthalate moiety were observed in **6** (Figure S4). It is important to note that each of the S_6-corona[3]arene[3]tetrazine and S_6-corona[3]arene[3]pyrid-

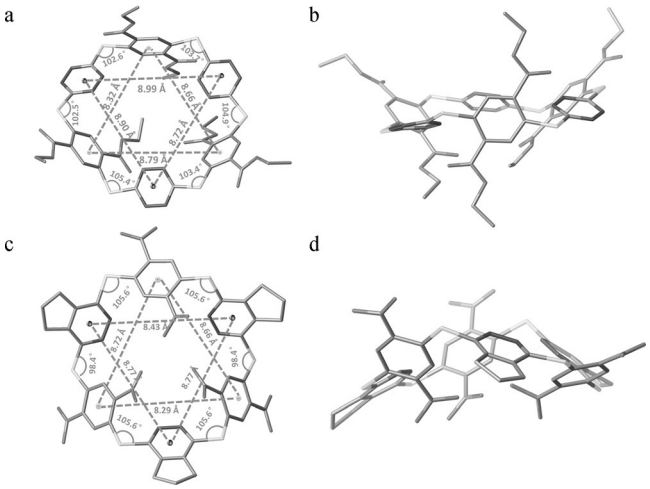


Figure 1. X-ray molecular structures of a,b) **3b** and c,d) **6** with top (a and c) and side (b and d) views. All hydrogen atoms and solvent molecules were omitted for clarity.

azine products gives a single set of simple proton and carbon resonance signals in its ^{1}H and ^{13}C NMR spectra, respectively, at room temperature and even at −60 °C (Figures S1 and S2). The outcomes indicated probably the presence of a highly symmetric structure. Most likely, there was a mixture of conformers which were able to undergo very rapid inter-conversions at the temperature of NMR prober relative to the NMR time-scale.

To explore the molecular recognition properties of water-soluble S_6-corona[3]arene[3]pyridazine compounds, interactions of **8** with dibromide salts of **G1** to **G4** (Figure 2) in aqueous media were studied by means of UV/Vis spectrometric titration. In comparison, intermolecular interactions of **4b** with the hexafluorophosphate salts of **G1–G4** (Figure 2) in organic phase were also examined. Figures 3 a and S5 show that the interactions of **8** with **G1–G4** in water and of **4b** with **G1–G4** in a mixture of CH_3CN and CH_2Cl_2 (v:v = 1:1) resulted in the color change of the guest solutions, suggesting a charge-transfer effect between hosts and guests. The formation of charge-transfer complexes was supported by UV/Vis spectra. For instance, the titration of hosts **8** and **4b** with **G1–G4** led to the increase of absorption at 400 nm to 450 nm (Figures 3 b and S6–S13). In the case of the inter-

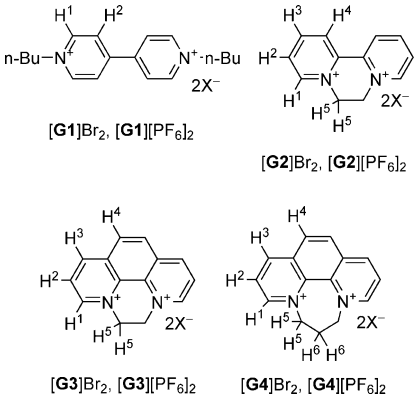


Figure 2. Structures of dicationic guest species **G1–G4**.

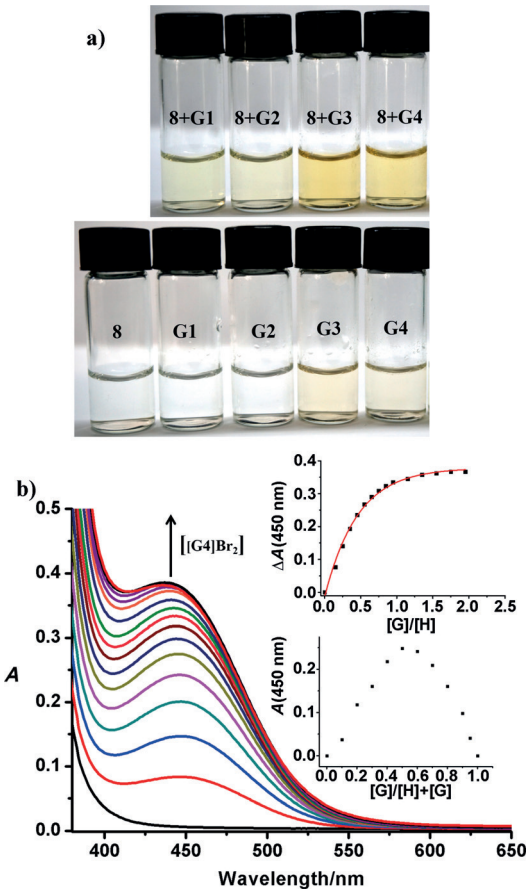


Figure 3. a) Color change after mixing host **8** with **G1**–**G4** in water. b) UV/Vis titration spectra at 20 °C of **8** (0.8 mmol L^{-1}) with addition of 0–1.95 equiv of **G4** (from bottom to top). The insets show a plot of ΔA (450 nm) against [**G4**]/[**8**] (top) and Job's plot (bottom).

actions between **8** and **G3** (Figure S8) and **G4** (Figure 3b), a salient new and broad charge-transfer absorption band at 450 nm was evidenced. The Job's plot experiments (Figures 3b and S6–S13) indicated the formation of 1:1 complexes due to probably the envelopment of a dicationic guest by a macrocyclic cavity of the host. Based on the outcomes of spectrometric titrations (Figures 3b and S6–S13), the association constants were calculated following a standard method using the Hyperquad2003 software.[22]

To shed further light on the molecular recognition of macrocycles **8** and **4b** towards dicationic species **G1**–**G4**, host–guest interactions were scrutinized using ^{1}H NMR spectroscopy. It was found that addition of **8** and **4b** into the aqueous and organic solutions of **G1**–**G4**, respectively, led to the up-field shifts of all proton signals of the guests. In the presence of equimolar macrocyclic host, for example, large $-\Delta\delta$ values for aromatic proton signals were observed (Figures 4, 5, and S15–S22). Significant shielding effect of a host on a guest, along with the evidence of the formation of a 1:1 host–guest complex (Figures S6–S12 and S24–S29) suggested envelopment of a dicationic guest by a macrocyclic host. It was also noteworthy that the interactions between **8** and **G1** and **G2**, and between **4b** and **G1**–

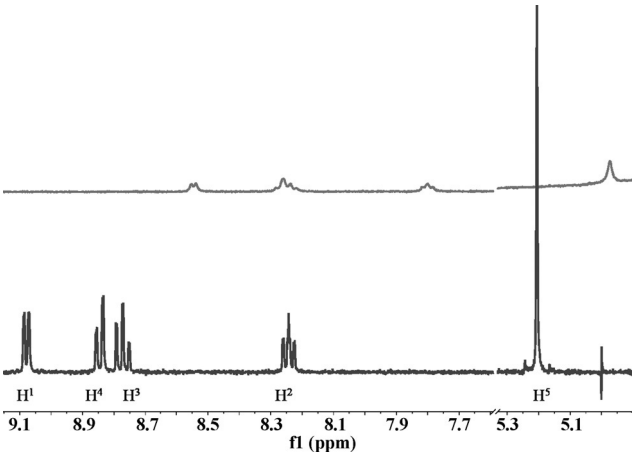


Figure 4. ^{1}H NMR spectra of **G2** (bottom) and of a mixture of equimolar **G2** and **8** (top) in D_2O at 297 K.

G4 afforded a single set of simple proton signals in their ^{1}H NMR spectra (Figures 4, S15, and S19–S22), indicating fast exchange processes for the complexation of **8** with **G1** and **G2**, and for that of **4b** with **G1**– **G4**. These results are in accordance with the weak host–guest interactions measured [$K_a < (4.60 \pm 0.06) \times 10^3\,\text{M}^{-1}$] (Table 1). On the contrary, two different sets of proton signals were observed in ^{1}H NMR spectra recorded from the solutions of **G3** and **G4** containing equimolar **8** (Figures 5 and S16). It was most probably the strong binding between **8** and **G3** [$K_a = (9.91 \pm 0.50) \times 10^4\,\text{M}^{-1}$] and between **8** and **G4** [$K_a = (1.18 \pm 0.06) \times 10^5\,\text{M}^{-1}$] that account for slow exchange rates relative to the NMR timescale. Moreover, careful scrutiny of ^{1}H NMR spectra of the complexes of **8** with **G3** and **G4** revealed that there were one set of simple proton signals of higher intensity and one set of complicated proton signals of lower intensity based on 2D COSY spectroscopy (Figures S17 and S18). While the simple set of spectrum was assigned to the guest that was symmetrically complexed by the host, the other complicated one was in agreement with the structure of the guest that was interacted with the host in an unsymmetric fashion. In other words, macrocyclic host **8** formed most likely in water two different types of host–guest complexes in which a guest species adopts different orientations in the cylindroid cavity.

A single crystal of **8**–**G2** inclusion complex was obtained by diffusing tetrahydrofuran into a mixture of **8** and **G2** in water solution. The X-ray crystallography shows unambiguously that 6,7-dihydrodipyrido[1,2-*a*:2′,1′-*c*]pyrazine-5,8-diium is located in the cavity of macrocyclic host (Figure 6).[21] Notably, in comparison to the structure illustrated in Figure 1c and d, the parent macrocycle self-regulated its cavity to complex the guest.

Table 1: Association constants (K_a) for 1:1 complexes between hosts and guests at 293 K.

	G1	G2	G3	G4
8[a]	$(1.10 \pm 0.06) \times 10^3$	$(4.60 \pm 0.23) \times 10^3$	$(9.91 \pm 0.50) \times 10^4$	$(1.18 \pm 0.06) \times 10^5$
4b[b]	$(3.62 \pm 0.18) \times 10^2$	$(2.21 \pm 0.11) \times 10^3$	$(2.51 \pm 0.12) \times 10^3$	$(2.54 \pm 0.13) \times 10^3$

[a] Measured in water. [b] Measured in a mixture of CH_3CN and CH_2Cl_2 (v:v = 1:1).

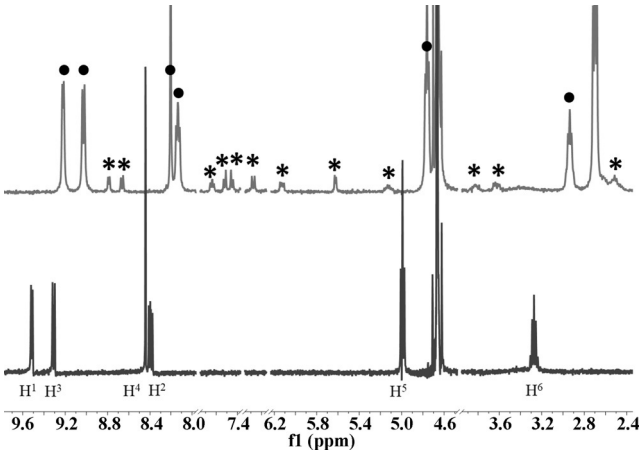


Figure 5. ^{1}H NMR spectra of **G4** (bottom) and of a mixture of equimolar **G4** and **8** (top) in D_2O at 293 K. Two different sets of proton signals, which are labeled with dots and stars, respectively, were observed in the spectrum recorded from a solution of **G4** and **8**.

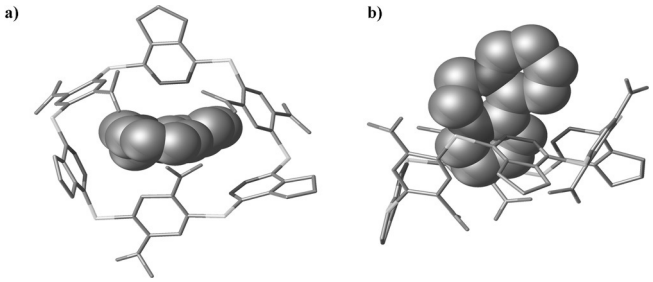


Figure 6. Structures of **G2**-**8** complex with a) top and b) side views. All hydrogen atoms, sodium ions, anions and solvent molecules were omitted for clarity.

In conclusion, we have reported the efficient and scalable synthesis of water-soluble S_6-corona[3]arene[3]pyridazines. The synthesis comprises a one-pot macrocyclic condensation reaction between 2,5-dimercaptoterephthalate and 3,6-dichlorotetrazine followed by the inverse electron-demand Diels–Alder reaction of tetrazine with an enamine and exhaustive saponification of esters. The resulting novel macrocyclic compounds, which adopt almost 1,3,5-alternate conformation in the crystalline state, were able to form 1:1 complexes with dicationic guests selectively in water with association constants ranging from $(1.10 \pm 0.06) \times 10^3\,\text{M}^{-1}$ to $(1.18 \pm 0.06) \times 10^5\,\text{M}^{-1}$. The easy availability, large cavity size, strong and selective binding power would render the water-soluble S_6-corona[3]arene[3]pyridazines useful macrocyclic hosts in various disciplines of supramolecular chemistry. Investigation of the nature of molecular recognition of novel S_6-corona[6](het)arenes and their applications are being actively pursued in this laboratory, and results will be published in due course.

Keywords: corona-arenes · host–guest systems · macrocycles · molecular recognition · paraquat

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 8386–8389
Angew. Chem. **2015**, *127*, 8506–8509

[1] *Comprehensive Supramolecular Chemistry* (Eds.: J.-M. Lehn, J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle), Pergamon, Oxford, **1996**.
[2] C. J. Pedersen, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021; *Angew. Chem.* **1988**, *100*, 1053.
[3] J.-M. Lehn, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89; *Angew. Chem.* **1988**, *100*, 91.
[4] D. J. Cram, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009; *Angew. Chem.* **1988**, *100*, 1041.
[5] C. J. Easton, S. F. Lincoln, *Modified Cyclodextrins. Scaffolds and Templates for Supramolecular Chemistry*, Imperial College Press, London, **1999**.
[6] a) C. D. Gutsche, *Calixarenes Revisited*, The Royal Society of Chemistry, Cambridge, **1998**; b) P. A. Gale, P. Anzenbacher, J. L. Sessler, *Coord. Chem. Rev.* **2001**, *222*, 57; c) J. Rebek, *Angew. Chem. Int. Ed.* **2005**, *44*, 2068; *Angew. Chem.* **2005**, *117*, 2104.
[7] J. W. Steed, D. R. Turner, K. J. Wallace, *Core Concepts in Supramolecular Chemistry and Nanochemistry*, Wiley, Chichester, **2007**.
[8] F. Huang, L. Isaacs, *Acc. Chem. Res.* **2014**, *47*, 1923.
[9] D. J. Cram, M. E. Tanner, R. Thomas, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1024; *Angew. Chem.* **1991**, *103*, 1048.
[10] T. Iwasawa, R. J. Hooley, J. Rebek, *Science* **2007**, *317*, 493.
[11] H. Zhang, B. Yao, L. Zhao, D.-X. Wang, B.-Q. Xu, M.-X. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 6326.
[12] a) M.-X. Wang, H.-B. Yang, *J. Am. Chem. Soc.* **2004**, *126*, 15412; b) M.-X. Wang, X.-H. Zhang, Q.-Y. Zheng, *Angew. Chem. Int. Ed.* **2004**, *43*, 838; *Angew. Chem.* **2004**, *116*, 856; c) M.-X. Wang, *Chem. Commun.* **2008**, 4541; d) M.-X. Wang, *Acc. Chem. Res.* **2012**, *45*, 182; e) N. Morohashi, F. Narumi, N. Iki, T. Hattori, S. Miyano, *Chem. Rev.* **2006**, *106*, 5291; f) W. Maes, W. Dehaen, *Chem. Soc. Rev.* **2008**, *37*, 2393; g) H. Tsue, K. Ishibashi, R. Tamura, *Top. Heterocycl. Chem.* **2008**, *17*, 73.
[13] a) T. Ogoshi, S. Kanai, S. Fujinami, T. Yamagishi, Y. Nakamoto, *J. Am. Chem. Soc.* **2008**, *130*, 5022; b) D.-R. Cao, Y.-H. Kou, J.-Q. Liang, Z.-Z. Chen, L.-Y. Wang, H. A. Meier, *Angew. Chem. Int. Ed.* **2009**, *48*, 9721; *Angew. Chem.* **2009**, *121*, 9901; c) M. Xue, Y. Yang, X. Chi, Z, Zhang, F. Huang, *Acc. Chem. Res.* **2012**, *45*, 1294.
[14] a) D.-X. Wang, Q.-Y. Zheng, Q.-Q. Wang, M.-X. Wang, *Angew. Chem. Int. Ed.* **2008**, *47*, 7485; *Angew. Chem.* **2008**, *120*, 7595; b) D.-X. Wang, M.-X. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 892.
[15] Q.-H. Guo, Z.-D. Fu, L. Zhang, M.-X. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 13548; *Angew. Chem.* **2014**, *126*, 13766.
[16] K. L. Kaplan, W. D. Reents, Jr., *Tetrahedron Lett.* **1982**, *23*, 373.
[17] J. Franke, F. Vögtle, *Tetrahedron Lett.* **1984**, *25*, 3445.
[18] V. A. Sergeev, V. I. Nedel'kin, A. V. Astankov, A. V. Nikiforov, E. M. Alov, Yu. A. Moskvichev, *Bull. Acad. Sci. USSR* **1990**, *39*, 763.
[19] E. Tsuchida, K. Miyatake, K. Yamamoto, A. S. Hay, *Macromolecules* **1998**, *31*, 6469.
[20] D. A. Zimmerman, J. L. Koenig, H. Ishida, *Polymer* **1996**, *37*, 3111.
[21] CCDC 1049268 (**3b**), 1049269 (**5**), and 1049343 (**G2**–**8** complex) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[22] a) P. Gans, A. Sabatini, A. Vacca, *Talanta* **1996**, *43*, 1739; b) Protonic Software, Hyperquad2003, http://www.hyperquad.co.uk.

Received: April 7, 2015
Published online: June 3, 2015

