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Communication

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Reversibly Tunable Lower Critical Solution Temperature Utilizing Host–Guest Complexation of Pillar[5]arene with Triethylene Oxide Substituents

Tomoki Ogoshi,* Ryohei Shiga, and Tada-aki Yamagishi

Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

Supporting Information

ABSTRACT: A thermoresponsive macromolecule consisting of 10 outer triethylene oxide groups and a pillar[5]arene core was prepared. The macromolecule showed lower critical solution temperature behavior. Moreover, its clouding point can be reversibly tuned based on the addition of guest and host compounds; the clouding point increased upon addition of a guest didecylviologen salt and decreased when the competitive host cucurbit[7]uril was added.

Poly(*N*-isopropylacrylamide) (pNIPAAm) is a well-known thermoresponsive polymer, showing a lower critical solution temperature (LCST) at 32 °C in aqueous media.[1−18] Using the LCST behavior of pNIPAAm, thermosensitive pNIPAAm-based materials have been prepared for applications such as controlled drug release,[2] molecular separation,[3] and tissue culture substrates.[4] The next direction in thermosensitive materials was creation of new generation thermosensitive materials possessing additional functions,[19−23] to replace pNIPAAm. In this Communication, we report a new smart thermosensitive macromolecule containing a macrocyclic structure in its core. Pillar[5]arenes[24−36] (Figure 1a), which are new macrocyclic hosts and were first reported by our group,[24] were used as the macrocyclic core. Because of their symmetrical pillar architecture,[24−26] facile and high-yield synthesis,[27] interesting host–guest property,[24,28−34] and planar chirality,[32] the chemistry of pillar[5]arenes has developed rapidly. One of the features of pillar[5]arenes is their high functionality.[34−36] Pillar[5]arenes have 10 reactive sites at their rims, and the presence of functional groups at the reactive sites significantly affects their physical properties.[28,30,35,36] In the present study, we present a pillar[5]arene derivative bearing triethylene oxide chains (Figure 1a, **2**) that exhibits LCST behavior. Because **2** contains the macrocyclic structure of pillar[5]arene, it is able to capture guest molecules. We demonstrate reversible tuning of the LCST using host–guest complexation.

Pillar[5]arenes modified with oligoethylene oxide groups (Figure 1a; **1**, n = 1; **2**, n = 3) were prepared by etherification of *per*-hydroxylated pillar[5]arene. A model unit was also synthesized[37] (Figure 1b, **2-model**) to evaluate how a cyclic structure affects the properties of **2**. The long triethylene oxide chains of **2** and **2-model** made them fully soluble in water at 25 °C. Conversely, **1** with short ethylene oxide chains was insoluble in water. Modification of the long hydrophilic triethylene oxide moieties is necessary to solubilize pillar[5]arene in water.

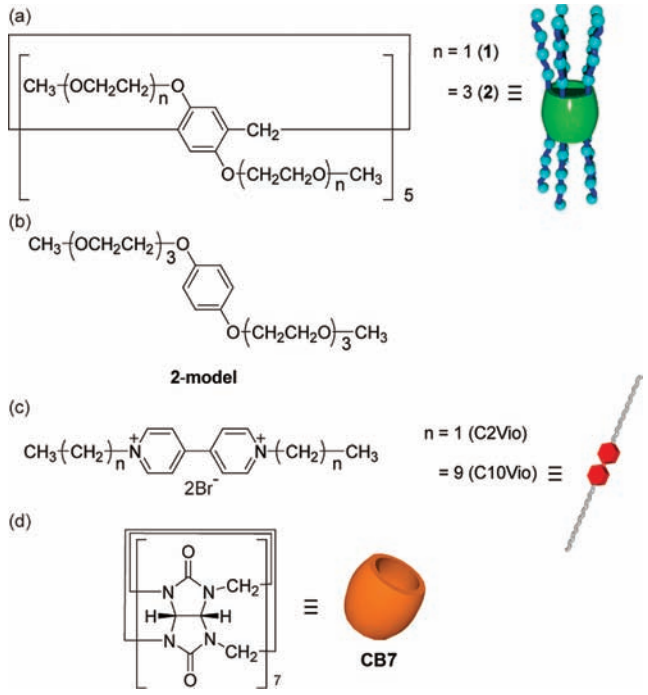

Figure 1. Chemical structures of (a) pillar[5]arenes modified with oligoethylene oxide groups, (b) unit model, (c) viologen derivatives, and (d) cucurbit[7]uril.

Interestingly, the clear aqueous solution of **2** at room temperature (Figure 2a) became opaque on heating (Figure 2b) and then

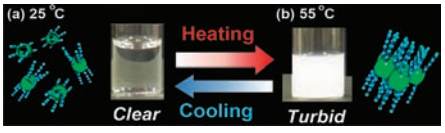

Figure 2. Photographs of an aqueous solution of **2** (2 mM) at (a) 25 and (b) 55 °C.

became clear again when the solution was cooled. That is, the turbidity change was reversible. This indicates that **2** exhibits LCST behavior in water. This phenomenon was not observed for **2-model** even on heating (Figure S3), suggesting that the

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pillar-shaped macrocyclic structure and modification with 10 triethylene oxide groups led to the LCST behavior. The LCST behavior of **2** can be attributed to the combination of the hydrophilic triethylene oxide moieties with the hydrophobic pillar[5]arene backbone (aromatic and methylene bridges). At temperatures above the clouding point (T_{cloud}), interaction of the hydrophobic groups causes **2** to aggregate and then separate from water. T_{cloud} was determined by the change in transmission at 650 nm on a temperature-controlled UV−vis spectrometer. On heating, T_{cloud} of **2** in 2 mM aqueous solution was found to be 42 °C, with the whole event taking place within 2 °C (Figure 3a,

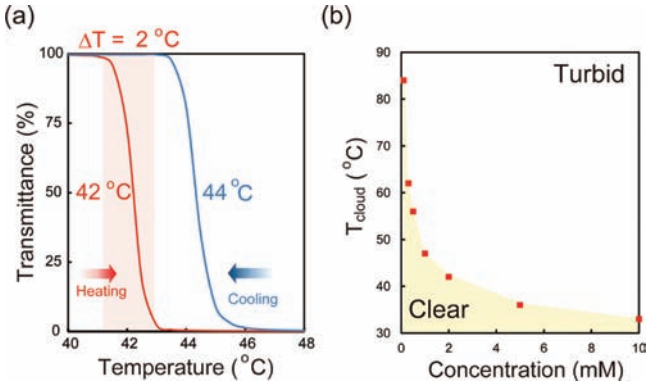

Figure 3. (a) Temperature dependence of light transmittance of **2** (2 mM) in aqueous solution (red line, heating process; blue line, cooling process). (b) Concentration dependence of the clouding point (T_{cloud}) of **2** in aqueous solution.

red line). The thermal transition of the cooling process was observed at 44 °C (Figure 3a, blue line). Hysteresis between the heating and cooling processes was very narrow (2 °C). Such sharp transition and narrow hysteresis seem to be a common feature of LCST of well-defined ethylene oxide branched macromolecules.[23] As the concentration of **2** increased, T_{cloud} decreased (Figure 3b), indicating that T_{cloud} depended the concentration of **2**. The trend is same with the other molecules showing T_{cloud}.[38] The average hydrodynamic diameter (D_H) of **2** as a function of temperature was investigated by dynamic light scattering (DLS) studies. Below T_{cloud} (25 °C), the D_H of **2** was 151 ± 16 nm (Figure S4), indicating that **2** forms an assembled structure. Above T_{cloud} (50 °C), the D_H of **2** increased to 799 ± 68 nm (Figure S5), indicating that **2** forms a large aggregate structure above T_{cloud}.

Pillar[5]arenes have a highly symmetrical cylindrical structure with a π-electron-rich cavity, so they are an ideal host for π-electron-poor guests such as viologens, pyridinium cations, and quaternary ammonium salts.[24,28−34] In this study, water-soluble viologen derivatives such as diethylviologen dibromide (Figure 1c, C2Vio) and didecylviologen dibromide (Figure 1c, C10Vio) were used as guests. Addition of C10Vio to **2** in water changed the color of the solution from clear to yellow, whereas C2Vio did not change the color of the solution of **2** (Figure S6). This indicates that **2** formed a charge-transfer (CT) complex with C10Vio but not with C2Vio. Multiple interactions such as CT and hydrophobic interactions should stabilize the host−guest complex because aqueous media were used as a solvent. In C2Vio, the hydrophobic interaction between C2Vio and **2** should be weaker than that between C10Vio and **2** because of the short hydrophobic alkyl chain of C2Vio compared to C10Vio. Based on the intensities of the CT bands, the stoichiometry of the CT complex determined from a Job plot was 1:1 (Figure S7), and the association constant (K) for the CT complex was (4.3 ± 0.5) × 10^3 M^{-1} at 25 °C (Figure S8). Inclusion of the viologen moiety of C10Vio into the cavity of **2** was confirmed by ^{1}H NMR measurements. When C10Vio was mixed with **2**, upfield shifts were observed for the proton signals from viologen and methylene protons adjacent to N atoms, whereas the other resonance bands hardly changed (Figure S9). The same ^{1}H NMR spectral changes were also observed for the host−guest complexes between pillar[5]-arene and viologen derivatives.[24,29,31] These results confirm the formation of a host−guest complex between **2** and C10Vio.

The effect of host−guest complexation on T_{cloud} was investigated. As the concentration of C10Vio increased, T_{cloud} gradually increased while maintaining sharp transitions (Figure 4a).

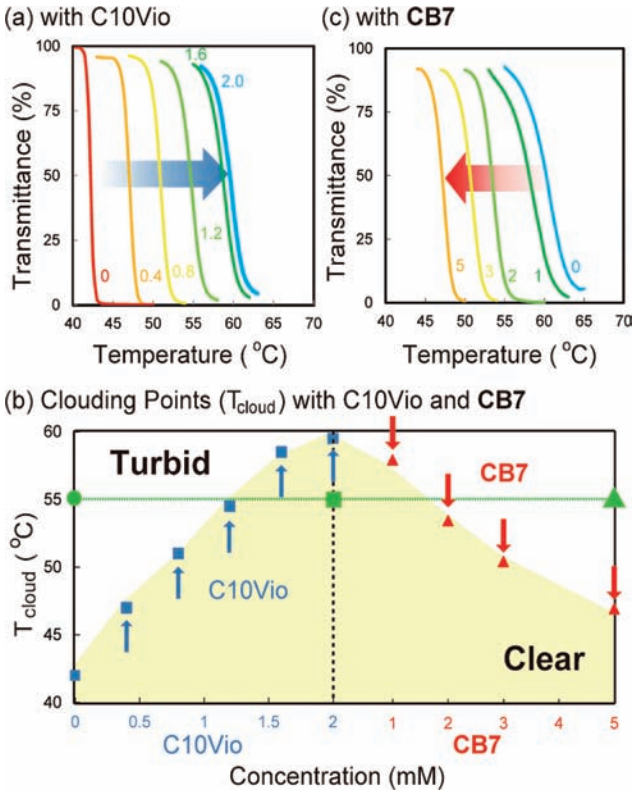

Figure 4. (a) Temperature dependence of light transmittance of an aqueous solution of **2** (2 mM) upon addition of C10Vio (0−2 mM) on heating. (b) Change in T_{cloud} upon addition of C10Vio and **CB7** to an aqueous solution of **2**. (c) Temperature dependence of light transmittance of a mixture of **2** (2 mM) and C10Vio (2 mM) in aqueous solution upon addition of **CB7** (0−5 mM) on heating.

By controlling the amount of C10Vio added, T_{cloud} was successfully tuned from 42 to 60 °C (Figure 4b, blue arrows). K for the complex at T_{cloud} was obtained by extrapolation using van't Hoff analysis (Figure S10). As the temperature increased, K decreased due to a thermal dissociation. However, a high K was maintained even at the maximum T_{cloud} (extrapolated K at 60 °C was (3.4 ± 1.3) × 10^3 M^{-1}). ^{1}H NMR spectra of these solutions revealed that signals from free C10Vio species were not observed above T_{cloud} (Figure S11). These data indicate that dissociation of the complex does not occur in the range of T_{cloud} investigated. The concentration of salts sometimes affects LCST. However, a change in T_{cloud} was not observed upon addition of C2Vio (Figure S12). Thus, T_{cloud} is independent of the concentration of salts in the range investigated.

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These results suggest that the observed increase in T_{cloud} upon addition of C10Vio is mainly caused by host−guest complexation. Repulsive forces between the complexed cations might prevent aggregation of **2**.[39] Therefore, heating at high temperature should be needed to aggregate **2**-C10Vio complexes.

Viologen derivatives form highly stable 1:1 host−guest complexes with cucurbit[7]urils (Figure 1d, **CB7**, K of the complexes with viologen derivatives are generally greater than 10^5 M^{-1}) because of the good fit between the cavity of the host and the cross-section of the viologen.[40−42] Thus, we used **CB7** as a competitive host to exclude C10Vio from the cavity of **2**. When **CB7** was added to a solution containing the host−guest complex of C10Vio (2 mM) and **2** (2 mM), the yellow solution derived from the CT complex was diluted (Figure S13), indicating dissociation of the CT complex and association of C10Vio with **CB7**. Upon addition of **CB7**, T_{cloud} gradually decreased with sharp transitions (Figure 4c). By controlling the amount of **CB7** added, T_{cloud} was able to be tuned from 60 to 47 °C (Figure 4b, red arrows). T_{cloud} did not change by mixing **2** and **CB7** in the absence of C10Vio (Figure S14), suggesting that T_{cloud} of **2** is independent of **CB7**. These results indicate that dissociation of the hydrophilic CT complex between **2** and C10Vio led to the observed decrease of T_{cloud}. Overall, we reversibly controlled T_{cloud} of **2** using the guest C10Vio and the competitive host **CB7**.

Based on a host−guest system, we demonstrated chemically responsive reversible turbid-to-clear and clear-to-turbid transitions. When a solution of **2** (2 mM) was heated to 55 °C (Figure 4b, green circles), the solution became turbid (Figure 5a)

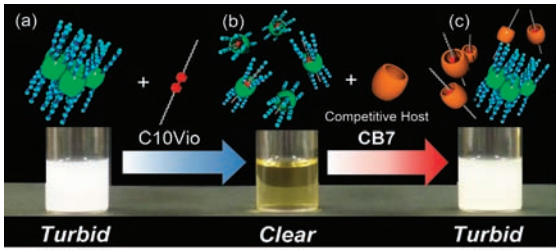

Figure 5. Photographs of (a) **2** (2 mM), (b) an equimolar mixture of **2** (2 mM) and C10Vio (2 mM), and (c) a mixture of **2** (2 mM), C10Vio (2 mM) and **CB7** (5 mM) in aqueous solution at 55 °C.

because the sample was heated above T_{cloud} (42 °C). Addition of C10Vio (2 mM) to the mixture at 55 °C (Figure 4b, green squares) caused the solution to change from turbid to clear (Figure 5b) because T_{cloud} of the CT complex of **2** with C10Vio is 60 °C. By mixing **CB7** (5 mM) into the mixture at 55 °C (Figure 4b, green triangles), the clear solution was changed again to turbid (Figure 5c). This is because T_{cloud} of the mixture of **2** (2 mM), C10Vio (2 mM), and **CB7** (5 mM) is 47 °C.

In conclusion, a new type of thermoresponsive material, macrocyclic compound (**2**) possessing excellent LCST behavior (sharp transition and narrow hysteresis) was successfully synthesized. This is the first examples of a themosensitive macrocyclic molecule, although LCST control by combination of pNIPAAm with host molecules has been reported.[5−13] Importantly, T_{cloud} of **2** can be readily adjusted from 42 to 60 °C upon addition of the guest C10Vio, and T_{cloud} was reversed back to that of pristine **2** upon addition of competitive host **CB7**. All systems in this study exhibited excellent thermoresponsive properties based on the host−guest system. The first-generation water-soluble pillar[5]-arenes[28,30] were charged and required a solution pH some distance from neutrality, which affected the electrolyte and water hardness, but nonionic water-soluble pillar[5]arene **2** overcomes these limitations and possesses the chemically responsive LCST behavior. Biocompatibility and T_{cloud} around body temperature are necessary to use thermosensitive materials as drug delivery systems (DDSs). Because T_{cloud} of **2** could be tuned around body temperature by optimizing its concentration and a large part of **2** was composed of biocompatible oligoethylene moieties, we believe that **2** shows great potential as a DDS. Moreover, the guest molecule C10Vio can be removed from water above T_{cloud}. Thus, the chemically responsive materials demonstrated in this study will be useful for cloud point extraction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section, characterization data, temperature dependence of light transmittance, DLS, UV−vis spectra, Job plot, van't Hoff plot, determination of association constants at various temperatures, and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

ogoshi@t.kanazawa-u.ac.jp

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Aseyev, V.; Tenhu, H.; Winnik, F. *Adv. Polym. Sci.* **2006**, *196*, 1−85.
(2) Piskin, E. *Int. J. Pharm.* **2004**, *277*, 105−118.
(3) Feil, H.; Bae, Y. H.; Feijen, J.; Kim, S. W. *J. Membr. Sci.* **1991**, *64*, 283−294.
(4) Takezawa, T.; Mori, Y.; Yoshizato, K. *Biotechnology* **1990**, *8*, 854−856.
(5) Ogoshi, T.; Masuda, K.; Yamagishi, T.; Nakamoto, Y. *Macromolecules* **2009**, *42*, 8003−8005.
(6) Yhaya, F.; Lim, J.; Kim, Y.; Liang, M.; Gregory, A. M.; Stenzel, M. H. *Macromolecules* **2011**, *44*, 8433−8445.
(7) Sambe, L. N.; Stoffelbach, F. O.; Lyskawa, J.; Delattre, F. O.; Fournier, D.; Bouteiller, L.; Charleux, B.; Cooke, G.; Woisel, P. *Macromolecules* **2011**, *44*, 6532−6538.
(8) Bigot, J.; Charleux, B.; Cooke, G.; Delattre, F. O.; Fournier, D.; Lyskawa, J. l.; Sambe, L. N.; Stoffelbach, F. O.; Woisel, P. *J. Am. Chem. Soc.* **2010**, *132*, 10796−10801.
(9) Amajjahe, S.; Ritter, H. *Macromolecules* **2008**, *41*, 3250−3253.
(10) Koopmans, C.; Ritter, H. *J. Am. Chem. Soc.* **2007**, *129*, 3502−3503.
(11) Bigot, J.; Fournier, D.; Lyskawa, J.; Marmin, T.; Cazaux, F.; Cooke, G.; Woisel, P. *Polym. Chem.* **2010**, *1*, 1024−1029.
(12) Rauwald, U.; del Barrio, J; Loh, X. J.; Scherman, O. A. *Chem. Commun.* **2011**, *47*, 6000−6002.
(13) Bigot, J.; Bria, M.; Caldwell, S. T.; Cazaux, F.; Cooper, A.; Charleux, B.; Cooke, G.; Fitzpatrick, B.; Fournier, D.; Lyskawa, J.; Nutley, M.; Stoffelbach, F.; Woisel, P. *Chem. Commun.* **2009**, 5266−5268.
(14) Plamper, F. A.; Schmalz, A.; Ballauff, M.; Müller, A. H. E. *J. Am. Chem. Soc.* **2007**, *129*, 14538−14539.
(15) Mao, H.; Li, C.; Zhang, Y.; Bergbreiter, D. E.; Cremer, P. S. *J. Am. Chem. Soc.* **2005**, *125*, 2850−2851.

(16) Klaikherd, A.; Nagamini, C.; Thayumanavan, S. *J. Am. Chem. Soc.* **2009**, *131*, 4830−4838.
(17) Zhang, Y.; Furyk, S.; Bergbreiter, D. E.; Cremer, P. S. *J. Am. Chem. Soc.* **2005**, *125*, 14505−14510.
(18) Bergbreiter, D. E.; Hughes, R.; Besinaiz, J.; Li, C.; Osburn, P. L. *J. Am. Chem. Soc.* **2003**, *125*, 8244−8249.
(19) Wang, F.; Klaikherd, A.; Thayumanavan, S. *J. Am. Chem. Soc.* **2011**, *133*, 13496−13503.
(20) Jia, Z.; Chen, H.; Zhu, X.; Yan, D. *J. Am. Chem. Soc.* **2006**, *128*, 8144−8145.
(21) Aathimanikandan, S. V.; Savariar, E. N.; Thayumanavan, S. *J. Am. Chem. Soc.* **2005**, *127*, 14922−14929.
(22) Betancourt, J. E.; Rivera, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 16666−16668.
(23) Roeser, J.; Moingeon, F.; Heinrich, B.; Masson, P.; Arnaud-Neu, F.; Rawiso, M.; Méry, S. *Macromolecules* **2011**, *44*, 8925−8935.
(24) Ogoshi, T.; Kanai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5022−5023.
(25) Ogoshi, T. *J. Incl. Phenom. Macroc. Chem.* **2011**, DOI: 10.1007/s10847-011-0027-2.
(26) Cragg, P. J.; Sharma, S. *Chem. Soc. Rev.* **2012**, *41*, 597−607.
(27) Ogoshi, T.; Aoki, T.; Kitajima, K.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Org. Chem.* **2011**, *76*, 328−331.
(28) Ogoshi, T.; Hashizume, M.; Yamagishi, T.; Nakamoto, Y. *Chem. Commun.* **2010**, *46*, 3708−3710.
(29) Li, C.; Xu, Q.; Li, J.; Yao, F.; Jia, X. *Org. Biomol. Chem.* **2010**, *8*, 1568−1576.
(30) Ma, Y.; Ji, X.; Xiang, F.; Chi, X.; Han, C.; He, J.; Abliz, Z.; Chen, W.; Huang, F. *Chem. Commun.* **2011**, *47*, 12340−12342.
(31) Strutt, N. L.; Zhang, H.; Giesener, M. A.; Lei, J.; Stoddart, J. F. *Chem. Commun.* **2012**, *48*, 1647−1649.
(32) Ogoshi, T.; Masaki, K.; Shiga, R.; Kitajima, K.; Yamagishi, T. *Org. Lett.* **2011**, *13*, 1264−1266.
(33) Zhang, Z.; Luo, Y.; Chen, J.; Dong, S.; Yu, Y.; Ma, Z.; Huang, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1397−1401.
(34) Strutt, N. L.; Forgan, R. S.; Spruell, J. M.; Botros, Y. Y.; Stoddart, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 5668−5671.
(35) Ogoshi, T.; Umeda, K.; Yamagishi, T.; Nakamoto, Y. *Chem. Commun.* **2009**, 4874−4876.
(36) Ogoshi, T.; Shiga, R.; Hashizume, M.; Yamagishi, T. *Chem. Commun.* **2011**, *47*, 6927−6929.
(37) Winkler, B.; Dai, L.; Mau, A. W. H. *Chem. Mater.* **1999**, *11*, 704−711.
(38) Afroze, F.; Nies, E.; Berghmans, H. *J. Mol. Struct.* **2000**, *554*, 55−68.
(39) Examples of dissociation of the supramolecular assemblies by complexation with charged guest molecules were reported. Ogoshi, T.; Takashima, Y.; Yamaguchi, H.; Harada, A. *Chem. Commun.* **2006**, 3702−3704. Ogoshi, T.; Hashizume, M.; Yamagishi, T.; Nakamoto, Y. *Langmuir* **2010**, *26*, 3169−3173.
(40) Ong, W.; Gómez-Kaifer, M.; Kaifer, A. E. *Org. Lett.* **2002**, *4*, 1791−1794.
(41) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844−4870.
(42) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H. J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621−630.