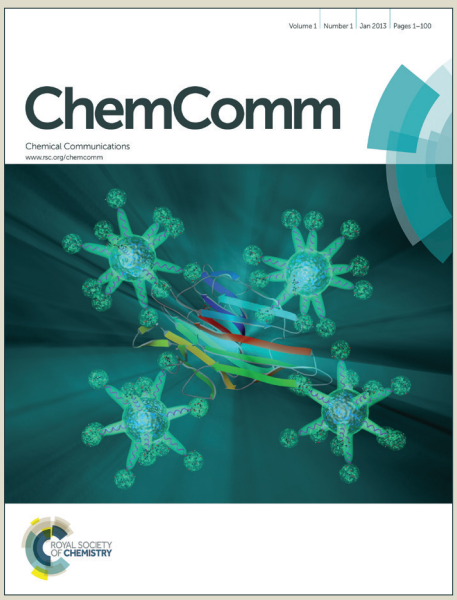
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Hydrophobic Monofunctionalized Cucurbit[7]uril Undergoes Self-Inclusion Complexation and Forms Vesicle-Type Assemblies

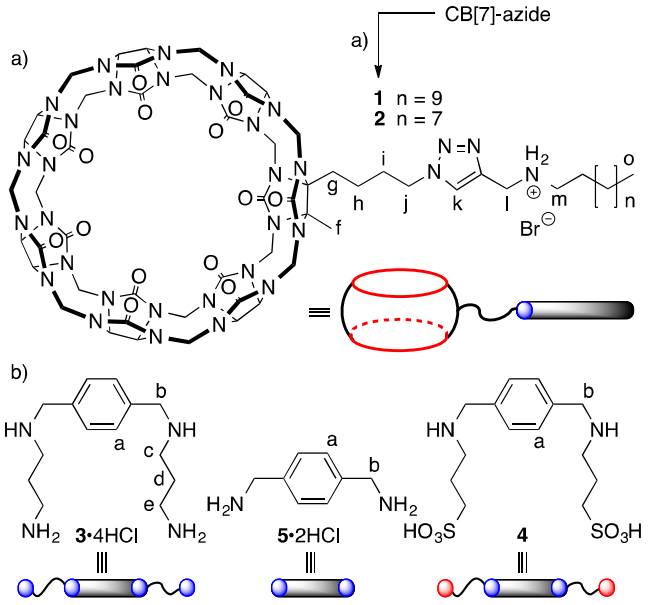
Yang Yu,[a] Jie Li,[a] Mingming Zhang,[b] Liping Cao*[a] and Lyle Isaacs*[b]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Hydrophobic monofunctionalized cucurbit[7]uril derivatives (1 and 2) were synthesized by clicking CB[7]-azide with propargylated alkylamines. Compounds 1 and 2 form self-inclusion complexes that are transformed into vesicle-type assemblies by addition of guests (3 – 5) as confirmed by ^{1}H and DOSY NMR, SEM, TEM, and fluorescence spectroscopy.

Molecular container compounds (e.g. crown ethers, cyclodextrins, cyclophanes, calixarenes)[1] encapsulate guest molecules and thereby change their fundamental molecular properties (e.g. chemical reactivity, electrochemistry, photophysical properties, vapour pressure) and have been exploited by supramolecular chemists in numerous application areas. In the past decade, the supramolecular chemistry of the cucurbit[n]uril (CB[n], n = 5, 6, i6, 7, i7, 8, 10, *t*14) family of molecular containers[2] has rapidly developed due to the availability of a homologous series of hosts which display tight binding, high selectivity, and stimuli responsive complexation behaviour toward cationic guests in aqueous solution.[3] Accordingly, unfunctionalized CB[n] have been used to create functional supramolecular systems including molecular machines, materials for capture and release of volatile compounds, supramolecular polymers, solubilizing agents for insoluble drugs, supramolecular catalysts, and chemical sensing ensembles.[3e,4] Accordingly, the development of new synthetic methods for the preparation of CB[n] derivatives and other CB[n]-type receptors are actively sought. For example, fully or partially alkyl and aryl substituted CB[n] have been prepared using combinations of glycoluril, substituted glycolurils, glycoluril dimer, and formaldehyde.[5] Cy_6CB[6] possesses improved solubility characteristics in organic solvents which allowed it to be used as a component in ion-selective electrodes.[5f] The use of analogues of glycoluril in the macrocyclization reaction delivers a variety of CB[n]-type molecular containers (e.g. CB[n] analogues,[6] hemicucurbit[n]urils,[7] bambus[n]urils,[8] and biotin[n]urils)[9,10]. Starving the CB[n] forming reaction of formaldehyde delivers methylene bridged glycoluril oligomers and nor-seco-CB[n] with exciting recognition properties (e.g. chiral recognition, metal ion triggered folding and assembly).[11] Capping of glycoluril oligomers with aromatic sidewalls delivers acyclic CB[n]-type receptors which are solubilizing agents for insoluble drugs and carbon nanotubes, and even function as an *in vivo* reversal agent for neuromuscular block induced by rocuronium.[12]



Scheme 1. a) Synthesis of **1** and **2**. Condition: a) $HCCCH_2NH(CH_2)_nCH_3$•HBr (**6** n = 9; **7** n = 11), Pericas' catalyst, H_2O, RT. b) Guests **3**-**5**.

However, it is the direct perhydroxylation of CB[n] to give $(HO)_{2n}$CB[n] developed by Kim has been most widely exploited in the creation of functional supramolecular systems including ion-channels,[13] materials for membrane protein fishing,[14] nanocapsules for targeted drug delivery,[15] and materials for tissue engineering.[16] Recently, two distinct approaches to monofunctionalized CB[n] derivatives have appeared. In one approach, the groups of Scherman and Kim controlled the hydroxylation reaction to yield $(HO)_1$CB[6] and $(HO)_1$CB[7] whose derivatives underwent self-inclusion and could be used to promote underwater adhesion.[17] In another approach, the groups of Isaacs and Sindelar used glycoluril hexamer as a building block for the synthesis of monofunctionalized CB[6] and CB[7] derivatives which can be used as components of sensing ensembles and for targeted drug delivery.[18] In this paper, we first report the preparation of hydrophobic monofunctionalized CB[7] derivatives **1** and **2** which feature covalently attached C_{10} or C_{12} alkyl chains, which can form self-inclusion complexes and vesicle-type assemblies induced by guests **4** and **5**.

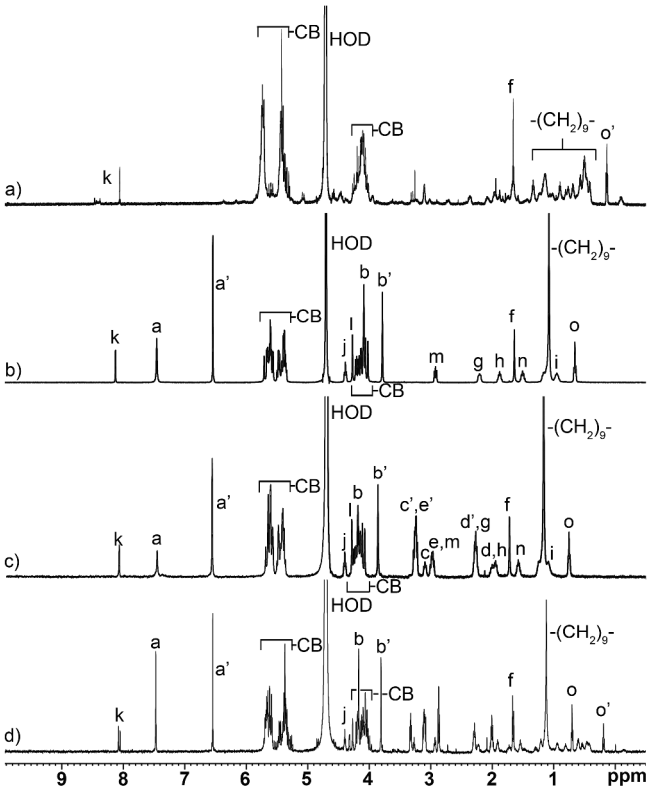


Figure 1. ^{1}H NMR spectra recorded (400 or 600 MHz, D_2O, RT) for: a) **1** (0.36 mM), b) **1** and **5** (1.9 equiv), c) **1** and **3** (1.5 equiv), and d) **1** and **4** (1.8 equiv).

As shown in Scheme 1, CB[7] derivatives **1** and **2** were synthesized by the reaction of CB[7]-azide[18c] with N-alkylpropargylamines **6** and **7** by 3+2 dipolar cycloaddition using Pericas' catalyst.[19] Compounds **1** and **2** feature a CB[7] container covalently connected to C_{10} or C_{12} alkyl ammonium groups. Because these alkylammonium ion tails are suitable guests for CB[7]-sized cavities we suspected that **1** and **2** would undergo self-association processes in water. Figure 1a shows the ^{1}H NMR spectrum recorded for **1** alone in D_2O at room temperature. Even though the spectrum is broadened and complex, diagnostic resonances for H_o (triplet at 0.32 ppm) and triazole H_k (singlet at 8.10) can be clearly recognized. On the other hand, the upfield region of the spectrum between 3.2 and 0.5 ppm, corresponding to the $(CH_2)_4$ linker between the CB[7] moiety and the triazole unit, and $(CH_2)_{11}$ of alkyl tail are broadened, which suggest the presence of self-assembly between the CB[7] cavity and the covalently attached ammonium ion tail. Figure 1b shows the ^{1}H NMR spectrum obtained upon addition of an excess of **5** which is a tight binder ($K_a \approx 10^9$ M^{-1}) toward CB[7].[3b] As expected, the ^{1}H NMR spectrum sharpens dramatically indicative of preferential inclusion of **5** in the CB[7] sized cavity of **1** to give the well defined tricationic assembly **1•5**. Analysis of the ^{1}H NMR chemical shifts establish that the C_{12} alkylmmonium ion tail and $(CH_2)_4$-triazolyl moieties are free in solution. The presence of resonances for free **5** and **1•5** in Figure 2b establish that the kinetics of guest exchange are slow on the ^{1}H NMR chemical shift timescale. Figure 1c shows the ^{1}H NMR spectra recorded for mixtures of **1** and tetracationic **3** which once again indicates the preferential inclusion of **3** within the CB[7] cavity within the well defined **1•3** assembly.

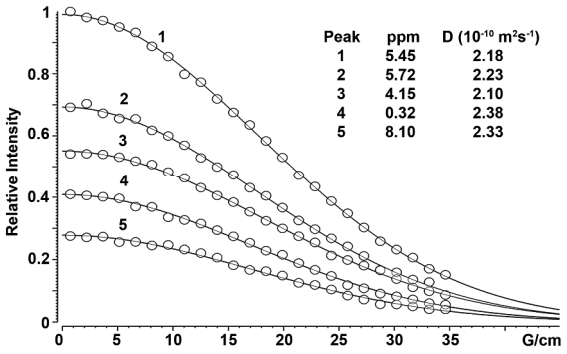
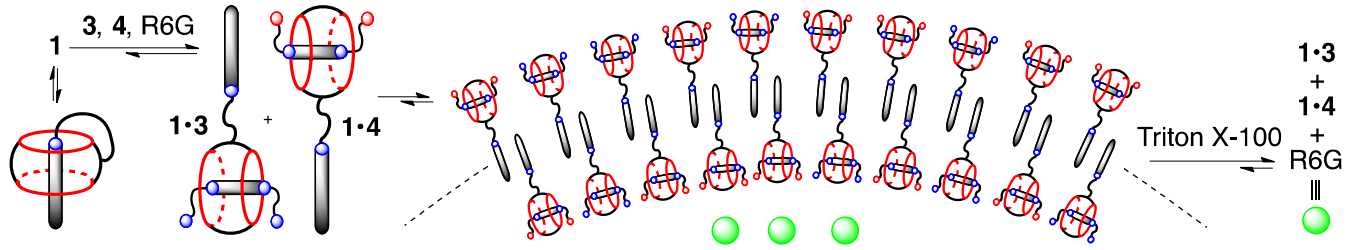


Figure 2. DOSY spectra recorded (600 MHz, D_2O, RT) for **1•5** and (b) self-complex **1** (0.32 mM).

We performed diffusion-ordered spectroscopy (DOSY) for **1•5** and $(\mathbf{1})_n$ (Figure 2) to gain insight into the degree of oligomerization of the self-assembled species $(\mathbf{1})_n$ (e.g. monomer, dimer, trimer, tetramer, polymer) in D_2O. The diffusion coefficients measured using 8 different resonances for $(\mathbf{1})_n$ and 5 different resonances for **1•5**, averaged $(2.26 \pm 0.10) \times 10^{-10}$ and $(2.24 \pm 0.14) \times 10^{-10}$ m^2 s^{-1}, respectively. The measured ratio of diffusion coefficients for **1•5** relative to $\mathbf{1}_n$ is 1.01, which strongly suggests the formation of the intramolecular self-inclusion complex (n = 1) in which the alkylammonium ion tail of **1** was encapsulated within its own CB[7] cavity (Figure S11). In contrast, the ^{1}H NMR spectrum of compound **2** alone shows two sharp resonances of the triazole H_k proton (integral ratio is about 67:33) are observed at 8.16 and 8.34 ppm (Figure S13) which is indicative of two different assemblies in slow exchange on the ^{1}H NMR timescale. The diffusion coefficient measured for most of the resonances of $(\mathbf{2})_n$ was clustered around $(2.29 \pm 0.13) \times 10^{-10}$ m^2 s^{-1} whereas the value for a monomeric **2•5** was $(2.44 \pm 0.08) \times 10^{-10}$ m^2 s^{-1} (Figure S15). The observed 6% decrease in diffusion coefficient is too small to indicate dimerization or higher order aggregation, and strongly suggests that the major species (67%) is the intramolecular self-inclusion complex. Surprisingly, the diffusion coefficient measured for the peak at 8.34 ppm was 1.64×10^{-10} m^2 s^{-1} (Supporting Information). For dimeric, trimeric, and tetrameric assemblies, theory predicts the ratios $D(\mathbf{2•5})/D(\mathbf{2}_n)$ = 1.260 (n = 2), 1.442 (n = 3), and 1.587 (n = 4). For the $\mathbf{2}_n$ assembly, the ratio of diffusion coefficients is 1.488, which is consistent with formation of the cyclic trimeric assembly $\mathbf{2}_3$; an MMFF minimized model of $\mathbf{2}_3$ is shown in Figure S12. Unfortunately, we could not study the aggregation states of these complexes as a function of concentration due to their low inherent solubility (< 0.4 mM).

Given the high level of interest in stimuli responsive supramolecular systems[20] we sought to create stimuli responsive systems based on **1** and **2**. The stimuli responsiveness (pH, chemical, electrochemical, photochemical) of CB[n] containers is well documented[4d,21] and has been used previously by Kim and Scherman to create responsive CB[8] amphiphile vesicles.[22] In our case, the chemical structure of **1** or **2** features a hydrophilic CB[7] head group covalently connected to a hydrophobic alkylammonium ion tail. Accordingly, we anticipated that **1** and **2** and their host-guest complexes would behave as supramolecular



Scheme 2. Illustration of the formation of supramolecular vesicles and the release of fluorescent dye.

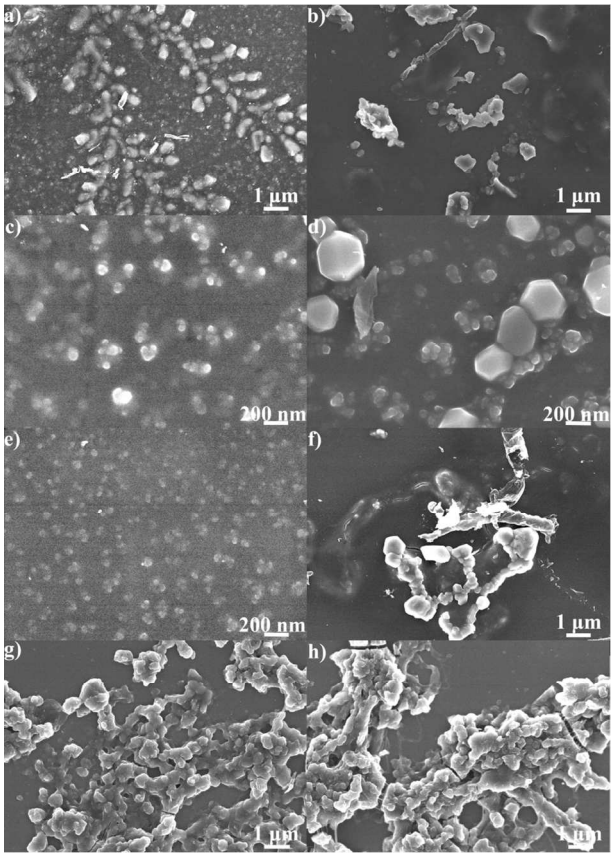


Figure 3. SEM images of: a) **1:3:4** = 1:1:0 (size range = 314 to 620 nm); b) **1:3:4** = 1:0.3:0.7 (aggregates); c) **1:3:4** = 1:0.4:0.6 (79 to 152 nm); d) **1:3:4** = 1:0.5:0.5 (90 to 414 nm); e) **1:3:4** = 1:0.6:0.4 (42 to 79 nm); f) **1:3:4** = 1:0.7:0.3 (aggregates); g) **1:3:4** = 1:0:1 (aggregates); h) **1** (aggregates). (Total concentration of **1** = 0.51 mM).

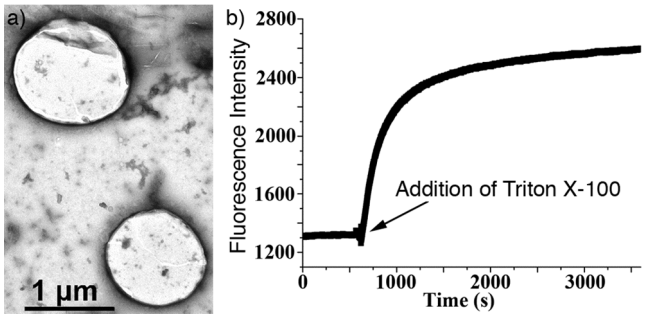


Figure 4. (a) TEM image of complexes **1•3** and **1•4** (**1**= 0.5 mM; **3** = 0.2 mM; **4** = 0.3 mM; samples were stained with uranyl acetate) and (b) Change in fluorescence emission intensity at 553 nm of rhodamine 6G triggered by addition of Triton X-100.

amphiphiles and assemble into micelles or vesicles in water.

Unfortunately, neither **1** nor **2** behave as amphiphiles in water because of their propensity to undergo self-inclusion complexation. To address this problem, we synthesized derivatives of p-xylylenediammonium ion **5** in the form of tetracationic guest **3** and zwitterionic guest **4** (Scheme 1b and Supporting Information). We anticipated that analogous to **1•5** would form the **1•3** and **1•4** complexes whose head groups feature pendant cationic NH_3^+ or anionic SO_3^- functional groups. The ^1H NMR spectra show that formation of the 1:1 complexes **1•3** and **1•4** also make the C_{12} alkyl tail of **1** free in solution (Figure 1c and 1d). We examined the self-assembled structures formed from different ratios of host-guest complexes **1•3** and **1•4** in the solid state by scanning electron microscopy (SEM). Similar to catanionic surfactant assemblies,[23] we find that mixtures of **1•3** and **1•4** host-guest complexes form different assemblies based on the mole fraction of the constituents (Figure 3 and S17). The assemblies formed from **1**:**3**:**4** (1:0.4:0.6) were selected for further structural investigation by transmission electron microscopy (TEM) measurements. A solution of **1**:**3**:**4** (1:0.4:0.6) was deposited on copper grids, followed by a slow evaporation in air at room temperature, followed by staining with uranyl acetate. The existence of spherical vesicles with a broad range of sizes (140 to 1200 nm) was observed by TEM. In Figure 4a, it was found that the spherical structures showed a clear contrast between the interior and periphery, which is typical characteristic behavior of vesicular structures. The thickness of the vesicle-like structure was calculated to be in the range of 7.3 – 46.8 nm from their TEM images (Figure S18) which suggests the presence of bilayer and multilayer type structures. Unfortunately, dynamic light scattering (DLS) studies were unsuccessful due to the appearance of precipitates.

The stimuli-responsive properties of the self-assembled vesicle structure can be used for encapsulation and the triggered release of active substances. Thus, we envisioned that this kind of supramolecular vesicle might be employed to encapsulate and release small molecules in aqueous solution. For this purpose, we mixed **1•3** and **1•4** with water-soluble fluorescent dye Rhodamine 6G (R6G) to prepare vesicles containing R6G. Figure 4b shows the fluorescence intensity of this system at 553 nm as a function of time. The fluorescence signal of the R6G encapsulated vesicles does not change over time in the absence of external stimuli. However, upon addition of Triton X-100, the collapse of the vesicles was triggered which results in an increase in fluorescence emission intensity (Figure 4b) over time. This result suggests that the dye undergoes aggregation induced quenching within the vesicle that is reversed when the dye is released (Figure 4b). As shown in Scheme 2, we believe that the addition of Triton X-100

resulted in the deaggregation of the hydrophobic assembly between alkyl tails into single host-guest complex with a concomitant release of the encapsulated R6G dye (Scheme 2).

In conclusion, we have demonstrated the synthesis and self-inclusion behavior of hydrophobic monofunctionalized CB[7] (**1** – **2**). Mixtures of the two stable host-guest complexes **1•3** and **1•4** – the act as supramolecular amphiphiles – results in the formation of vesicle-type assemblies. The fluorescent dye R6G can be loaded into the vesicles and released upon addition of Triton X-100. Given the well known stimuli responsiveness of CB[n]•guest complexes, we expect that other stimuli (e.g. chemical, electrochemical, pH) can be used to trigger disassembly of these supramolecular amphiphile vesicles. We expect that they may find applicability as components of biosensors, drug delivery systems, and for compartmentalized catalysis in water.

We thank the National Natural Science Foundation of China (21472149 to L.C.) and the US National Science Foundation (CHE-1110911 and CHE-1404911 to L.I.) for financial support. We also acknowledge the use of the facilities of the Maryland NanoCenter and its NispLab.

Notes and references

[a] *Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of the Ministry of Education, College of Chemistry and Materials Science, Northwest University, Xi'an, P. R. China. E-mail: chcaoliping@nwu.edu.cn*

[b] *Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742, USA. Fax: +1 301-314-9121; Tel: +1 301-405-1884; E-mail: LIsaacs@umd.edu*

† Electronic Supplementary Information (ESI) available: Experimental details of UV-Vis and NMR spectroscopy. See DOI: 10.1039/b000000x/

1) (a) C. D. Gutsche *Acc. Chem. Res.* **1983**, *16*, 161-170; (b) D. J. Cram *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009-1020; (c) F. Diederich *Angew. Chem., Intl. Ed. Engl.* **1988**, *27*, 362-386; (d) J.-M. Lehn *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89-112; (e) C. J. Pedersen *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021-1027.

2) (a) W. A. Freeman, W. L. Mock and N.-Y. Shih *J. Am. Chem. Soc.* **1981**, *103*, 7367-7368; (b) J. Kim, I.-S. Jung, S.-Y. Kim, E. Lee, J.-K. Kang, S. Sakamoto, K. Yamaguchi and K. Kim *J. Am. Chem. Soc.* **2000**, *122*, 540-541; (c) A. Day, A. P. Arnold, R. J. Blanch and B. Snushall *J. Org. Chem.* **2001**, *66*, 8094-8100; (d) A. I. Day, R. J. Blanch, A. P. Arnold, S. Lorenzo, G. R. Lewis and I. Dance *Angew. Chem., Int. Ed.* **2002**, *41*, 275-277; (e) L. Isaacs, S.-K. Park, S. Liu, Y. H. Ko, N. Selvapalam, Y. Kim, H. Kim, P. Y. Zavalij, G.-H. Kim, H.-S. Lee and K. Kim *J. Am. Chem. Soc.* **2005**, *127*, 18000-18001; (f) S. Liu, P. Y. Zavalij and L. Isaacs *J. Am. Chem. Soc.* **2005**, *127*, 16798-16799; (g) X. J. Cheng, L.-L. Liang, K. Chen, N.-N. Ji, X. Xiao, J.-X. Zhang, Y.-Q. Zhang, S.-F. Xue, Q.-J. Zhu, X.-L. Ni and Z. Tao *Angew. Chem. Int. Ed.* **2013**, *52*, 7252-7255.

3) (a) W. L. Mock and N.-Y. Shih *J. Org. Chem.* **1986**, *51*, 4440-4446; (b) S. Liu, C. Ruspic, P. Mukhopadhyay, S. Chakrabarti, P. Y. Zavalij and L. Isaacs *J. Am. Chem. Soc.* **2005**, *127*, 15959-15967; (c) L. Cao, M. Sekutor, P. Y. Zavalij, K. Mlinaric-Majerski, R. Glaser and L. Isaacs *Angew. Chem. Int. Ed.* **2014**, *53*, 988-993; (d) S. Moghaddam, C. Yang, M. Rekharsky, Y. H. Ko, K. Kim, Y. Inoue and M. K. Gilson *J. Am. Chem. Soc.* **2011**, *133*, 3570-3581; (e) S. Kasera, F. Biedermann, J. J. Baumberg, O. A. Scherman and S. Mahajan *Nano Lett.* **2012**, *12*, 5924-5928; (f) W. M. Nau, M. Florea and K. I. Assaf *Isr. J. Chem.* **2011**, *51*, 559-577; (g) K. I. Assaf and W. M. Nau *Chem. Soc. Rev.* **2015**, *44*, 394-418.

4) (a) Y. Miyahara, K. Abe and T. Inazu *Angew. Chem., Int. Ed.* **2002**, *41*, 3020-3023; (b) E. Appel, J. del Barrio, X. Loh and O. Scherman *Chem. Soc. Rev.* **2012**, *41*, 6195-6214; (c) A. Hennig, H. Bakirci and W. M. Nau *Nat. Methods* **2007**, *4*, 629-632; (d) Y. H. Ko, E. Kim, I. Hwang and K. Kim *Chem. Commun.* **2007**, 1305-1315; (e) S. Walker, R. Oun, F. J. McInnes and N. J. Wheate *Isr. J. Chem.* **2011**, *51*, 616-624; (f) B. C. Pemberton, R. Raghunathan, S. Volla and J. Sivaguru *Chem. Eur. J.* **2012**, *18*, 12178-12190; (g) X.-L. Ni, X. Xiao, H. Cong, Q.-J. Zhu, S.-F. Xue and Z. Tao *Acc. Chem. Res.* **2014**, *47*, 1386-1395.

5) (a) A. I. Day, A. P. Arnold and R. J. Blanch *Molecules* **2003**, *8*, 74-84; (b) Y. Zhao, S. Xue, Q. Zhu, Z. Tao, J. Zhang, Z. Wei, L. Long, M. Hu, H. Xiao and A. I. Day *Chin. Sci. Bull.* **2004**, *49*, 1111-1116; (c) H. Isobe, S. Sato and E. Nakamura *Org. Lett.* **2002**, *4*, 1287-1289; (d) S. Sasmal, M. K. Sinha and E. Keinan *Org. Lett.* **2004**, *6*, 1225-1228; (e) A. Flinn, G. C. Hough, J. F. Stoddart and D. J. Williams *Angew. Chem.* **1992**, *104*, 1550-1552; (f) J. Zhao, H.-J. Kim, J. Oh, S.-Y. Kim, J. W. Lee, S. Sakamoto, K. Yamaguchi and K. Kim *Angew. Chem., Int. Ed.* **2001**, *40*, 4233-4235; (g) F. Wu, L.-H. Wu, X. Xiao, Y.-Q. Zhang, S.-F. Xue, Z. Tao and A. I. Day *J. Org. Chem.* **2012**, *77*, 606-611.

6) J. Lagona, B. D. Wagner and L. Isaacs *J. Org. Chem.* **2006**, *71*, 1181-1190.

7) Y. Miyahara, K. Goto, M. Oka and T. Inazu *Angew. Chem. Int. Ed.* **2004**, *43*, 5019-5022.

8) (a) J. Svec, M. Necas and V. Sindelar *Angew. Chem., Int. Ed.* **2010**, *49*, 2378-2381; (b) M. Singh, E. Solel, E. Keinan and O. Reany *Chem. - Eur. J.* **2014**, Ahead of Print.

9) M. Lisbjerg, B. E. Nielsen, B. O. Milhoj, S. P. Sauer and M. Pittelkow *Org. Biomol. Chem.* **2015**, *13*, 369-373.

10) G. Parvari, S. Annamalai, I. Borovoi, H. Chechik, M. Botoshansky, D. Pappo and E. Keinan *Chem. Commun.* **2014**, *50*, 2494-2497.

11) (a) W.-H. Huang, S. Liu, P. Y. Zavalij and L. Isaacs *J. Am. Chem. Soc.* **2006**, *128*, 14744-14745; (b) W.-H. Huang, P. Y. Zavalij and L. Isaacs *Angew. Chem., Int. Ed.* **2007**, *46*, 7425-7427; (c) W.-H. Huang, P. Y. Zavalij and L. Isaacs *J. Am. Chem. Soc.* **2008**, *130*, 8446-8454; (d) W.-H. Huang, P. Y. Zavalij and L. Isaacs *Org. Lett.* **2008**, *10*, 2577-2580.

12) (a) D. Ma, G. Hettiarachchi, D. Nguyen, B. Zhang, J. B. Wittenberg, P. Y. Zavalij, V. Briken and L. Isaacs *Nat. Chem.* **2012**, *4*, 503-510; (b) D. Ma, B. Zhang, U. Hoffmann, M. G. Sundrup, M. Eikermann and L. Isaacs *Angew. Chem., Int. Ed.* **2012**, *51*, 11358-11362; (c) C. Shen, D. Ma, B. Meany, L. Isaacs and Y. Wang *J. Am. Chem. Soc.* **2012**, *134*, 7254-7257.

13) Y. J. Jeon, H. Kim, S. Jon, N. Selvapalam, D. H. Oh, I. Seo, C.-S. Park, S. R. Jung, D.-S. Koh and K. Kim *J. Am. Chem. Soc.* **2004**, *126*, 15944-15945.

14) D.-W. Lee, K. Park, M. Banerjee, S. Ha, T. Lee, K. Suh, S. Paul, H. Jung, J. Kim, N. Selvapalam, S. Ryu and K. Kim *Nat. Chem.* **2011**, *3*, 154-159.

15) E. Kim, D. Kim, H. Jung, J. Lee, S. Paul, N. Selvapalam, Y. Yang, N. Lim, C. G. Park and K. Kim *Angew. Chem., Int. Ed.* **2010**, *49*, 4405-4408.

16) (a) H. Jung, K. M. Park, J.-A. Yang, E. J. Oh, D.-W. Lee, K. Park, S. H. Ryu, S. K. Hahn and K. Kim *Biomaterials* **2011**, *32*, 7687-7694; (b) K. M. Park, J.-A. Yang, H. Jung, J. Yeom, J. S. Park, K.-H. Park, A. S. Hoffman, S. K. Hahn and K. Kim *ACS Nano* **2012**, *6*, 2960-2968.

17) (a) N. Zhao, G. Lloyd and O. A. Scherman *Chem. Commun.* **2012**, *48*, 3070-3072; (b) Y. Ahn, Y. Jang, N. Selvapalam, G. Yun and K. Kim *Angew. Chem., Int. Ed.* **2013**, *52*, 3140-3144.

18) (a) D. Lucas, T. Minami, G. Iannuzzi, L. Cao, J. B. Wittenberg, P. Anzenbacher and L. Isaacs *J. Am. Chem. Soc.* **2011**, *133*, 17966-17976; (b) L. Cao and L. Isaacs *Org. Lett.* **2012**, *14*, 3072-3075; (c) B. Vinciguerra, L. Cao, J. R. Cannon, P. Y. Zavalij, C. Fenselau and L. Isaacs *J. Am. Chem. Soc.* **2012**, *134*, 13133-13140; (d) L. Cao, G. Hettiarachchi, V. Briken and L. Isaacs *Angew. Chem., Int. Ed.* **2013**, *52*, 12033-12037; (e) L. Gilberg, M. S. A. Khan, M. Enderesova and V. Sindelar *Org. Lett.* **2014**, *16*, 2446-2449.

19) S. Ozcubukcu, E. Ozkal, C. Jimeno and M. Pericas *Org. Lett.* **2009**, *11*, 4680-4683.

20) (a) S. Dong, B. Zheng, F. Wang and F. Huang *Acc. Chem. Res.* **2014**, *47*, 1982-1994; (b) D.-S. Guo and Y. Liu *Acc. Chem. Res.* **2014**, *47*, 1925-1934; (c) X. Ma and H. Tian *Acc. Chem. Res.* **2014**, *47*, 1971-1981; (d) H. Yang, B. Yuan, X. Zhang and O. A. Scherman *Acc. Chem. Res.* **2014**, *47*, 2106-2115.

21) (a) L. Isaacs *Acc. Chem. Res.* **2014**, *47*, 2052-2062; (b) E. Masson, X. Ling, R. Joseph, L. Kyeremeh-Mensah and X. Lu *RSC Adv.* **2012**, *2*, 1213-1247.

22) (a) Y. J. Jeon, P. K. Bharadwaj, S. W. Choi, J. W. Lee and K. Kim *Angew. Chem. Int. Ed.* **2002**, *41*, 4474-4476; (b) D. Jiao, J. Geng, X. J. Loh, D. Das, T.-C. Lee and O. A. Scherman *Angew. Chem., Int. Ed.* **2012**, *51*, 9633-9637.

23) S. B. Lioi, X. Wang, M. R. Islam, E. J. Danoff and D. S. English *Phys. Chem. Chem. Phys.* **2009**, *11*, 9315-9325.