Chirality Induction

DOI: 10.1002/anie.200906248

A Tale of Three Carboxylates: Cooperative Asymmetric Crystallization of a Three-Dimensional Microporous Framework from Achiral Precursors**

*Jian Zhang, Shumei Chen, Ruben A. Nieto, Tao Wu, Pingyun Feng, and Xianhui Bu**

There is currently an enormous demand for practical synthetic methods to allow the preparation of chiral compounds as single enantiomers.[1,2] While homochirality is a ubiquitous feature in living systems, the generation of homochirality using chemical methods remains highly challenging.[3–5] For the synthesis of enantiopure or enantioenriched molecules, great progress has been achieved in the past several decades through the use of asymmetric homogeneous catalysts.[6] In comparison, there has been very little progress in the area of asymmetric crystallization from achiral precursors to form enantiopure or enantioenriched crystalline nanoporous materials. The latter are very important for the development of heterogeneous porous asymmetric catalysts based on crystalline solids.

In the past decade, there has been an increasing interest in creating crystalline homochiral porous materials that may be utilized for enantioselective catalysis, separation, and so forth.[1–3] The main objective is to devise homochiral 3D frameworks with tunable pore geometry and catalytic properties for enantioselective progress. With few exceptions, homochiral porous solids prepared to date acquired homochirality through the incorporation of enantiopure organic ligands that are bonded to the crystalline framework as either crosslinking or pendant ligands.[1–3,7–9]

In the absence of enantiopure building blocks, chirality can be generated from achiral precursors through crystallization, as evidenced by many crystals (such as quartz) reported in enantiomorphous space groups.[4] In these crystals, chirality comes from the spatial organization of achiral building blocks. While individual crystals can be homochiral through a process called spontaneous resolution, the bulk sample tends to be a conglomerate, an equal mixture of crystals with opposite handedness.[10]

It is worth emphasizing that the generation of chirality itself is usually not an asymmetric process (because of the formation of racemates) and is not uncommon either. In the area of homochiral crystalline porous materials, it is the generation of bulk homochirality from achiral building blocks that is still rare and highly challenging.[11] Several well-known examples of homochiral crystallization (sometimes also called total spontaneous resolution or symmetry breaking) from achiral precursors (e.g., $NaClO_3$) are known.[11a] However, these examples are based on statistical fluctuation of initial nucleation events (e.g., single-colony growth induced by secondary nucleation), and the particular handedness of crystals is not controllable. Such experiments, when repeated multiple times, would normally lead to an overall racemic product. In addition, crystals in these examples are not 3D porous materials.

One example in the control of the absolute chirality of porous materials built from achiral units was provided by Rosseinsky and co-workers, who showed that the absolute chirality of an intrinsically chiral three-connected net can be induced by the coordination of enantiopure solvent molecules to the framework.[12] More recently, controllable homochiral crystallization in 3D open-framework materials was demonstrated by Morris and co-workers through the use of a chiral ionic liquid solvent (1-butyl-3-methylimidazolium L-aspartate).[13] One unique and unprecedented aspect of the Morris group's work is that the handedness of the 3D framework materials is controlled without having any enantiopure ligand incorporated into the framework (neither bridging nor pendant). Complementary to the use of chiral ionic liquid solvents, naturally occurring enantiopure alkaloids such as cinchonidine and cinchonine were recently found to induce the homochiral crystallization of a metal–organic framework.[14]

Despite this progress, the controllable asymmetric crystallization of 3D open-framework materials from achiral precursors remains poorly explored. It is unlikely that a particular chiral induction reagent can induce absolute chirality in different types of chiral crystals. It is conceivable that the controlled asymmetric crystallization of a porous material with a particular composition and topology, if possible, would require a unique chiral induction agent. It is therefore essential to study what types of open-framework

[*] Dr. J. Zhang,[+] Dr. S. Chen,[+] R. A. Nieto, Prof. Dr. X. Bu
Department of Chemistry and Biochemistry
California State University, Long Beach
1250 Bellflower Boulevard, Long Beach, CA 90840 (USA)
Fax: (+1) 562-985-8557
E-mail: xbu@csulb.edu
Dr. J. Zhang[+]
State Key Laboratory of Structural Chemistry
Fujian Institute of Research on the Structure of Matter, CAS
Fuzhou, Fujian, 350002 (China)
T. Wu, Prof. Dr. P. Feng
Department of Chemistry, University of California
Riverside, CA 92521 (USA)
[+] These authors contributed equally to this work.

[**] We thank the support of this work by NIH (X.B. 2 S06 GM063119-05), NSF (X.B. DMR-0846958), and DOE (P.F. 004407-002). X.B. is a Henry Dreyfus Teacher Scholar.

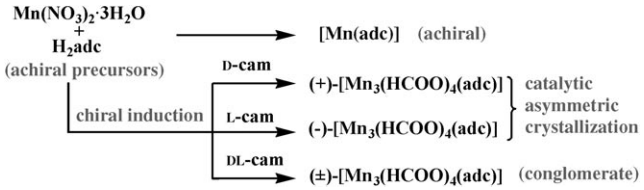
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200906248.

structures can be crystallized asymmetrically and with what kinds of chiral induction agents.

Herein, we explore the enantioselective effect of enantiopure organic acids and naturally occurring amino acids. The ultimate goal is to create a library of inexpensive chiral chemicals that can effect asymmetric crystallization of 3D crystalline porous materials and to use these inexpensive asymmetric molecular catalysts, such as organic acids and amino acids, to create new crystalline heterogeneous asymmetric catalysts. Furthermore, by exploring different types of chiral induction agents, it is possible to develop a better understanding of chemical or structural factors that contribute to the asymmetric crystallization.

Crystals of (+)-$[Mn_3(HCOO)_4(adc)]$ (denoted **1**D, H_2adc = adamantane-1,3-dicarboxylic acid) and (−)-$[Mn_3(HCOO)_4(adc)]$ (**1**L) were solvothermally synthesized (Scheme 1). They consist of a 3D Mn-O-Mn framework of $[Mn_3(HCOO)_4]_n^{2n+}$ units with honeycomb channels along the *c* axis. Decorative achiral organic chains of adc ligands line the honeycomb channels by attaching to the wall of $[Mn_3(HCOO)_4]_n^{2n+}$ through Mn–adc bonds (Figure 1 a,b,d). It is worth noting that $[Mn_3(HCOO)_4]_n^{2n+}$ is chiral and forms 3_1 or 3_2 helical structures along the *c* axis. The most interesting aspect of its synthesis is the asymmetric crystallization catalyzed by chiral additives (Figure 1 c). Furthermore, through a comparative study of four different crystallization processes with D-, L-, or DL-camphoric acid (H_2cam) and without additive (Scheme 1), we are able to gain a much better understanding of the chirality induction mechanism. The permanent microporosity of **1**D was characterized by the CO_2 adsorption isotherm, which shows a significant adsorption of 25.1 $cm^3 g^{-1}$ at approximately 1 atm and 273 K (Figure S5 in the Supporting Information).

Crystals of **1**D were found to be predominant in the batch synthesized using a small amount of enantiopure D-(+)-H_2cam as chiral catalyst, while crystals of **1**L were found to be predominant in the batch synthesized using a small amount of enantiopure L-(−)-H_2cam. Note that in both cases, enantiopure camphoric acid is not incorporated into the crystal structure. However, without camphoric acid, crystals of **1**D and **1**L cannot even be synthesized, much less their absolute chirality controlled.



Scheme 1. Illustration of four crystallization processes showing that the camphorate ligand not only controls the absolute chirality of crystals, but also enables and catalyzes the growth of chiral crystals. The synthesis and crystallization were performed in mixed DMF/EtOH solvents at 120 °C. The formate ligand was generated in situ from the solvent DMF.

To confirm the asymmetric crystallization, crystal structures of twenty crystals were randomly picked from the batch catalyzed with D-H_2cam and were analyzed using single-

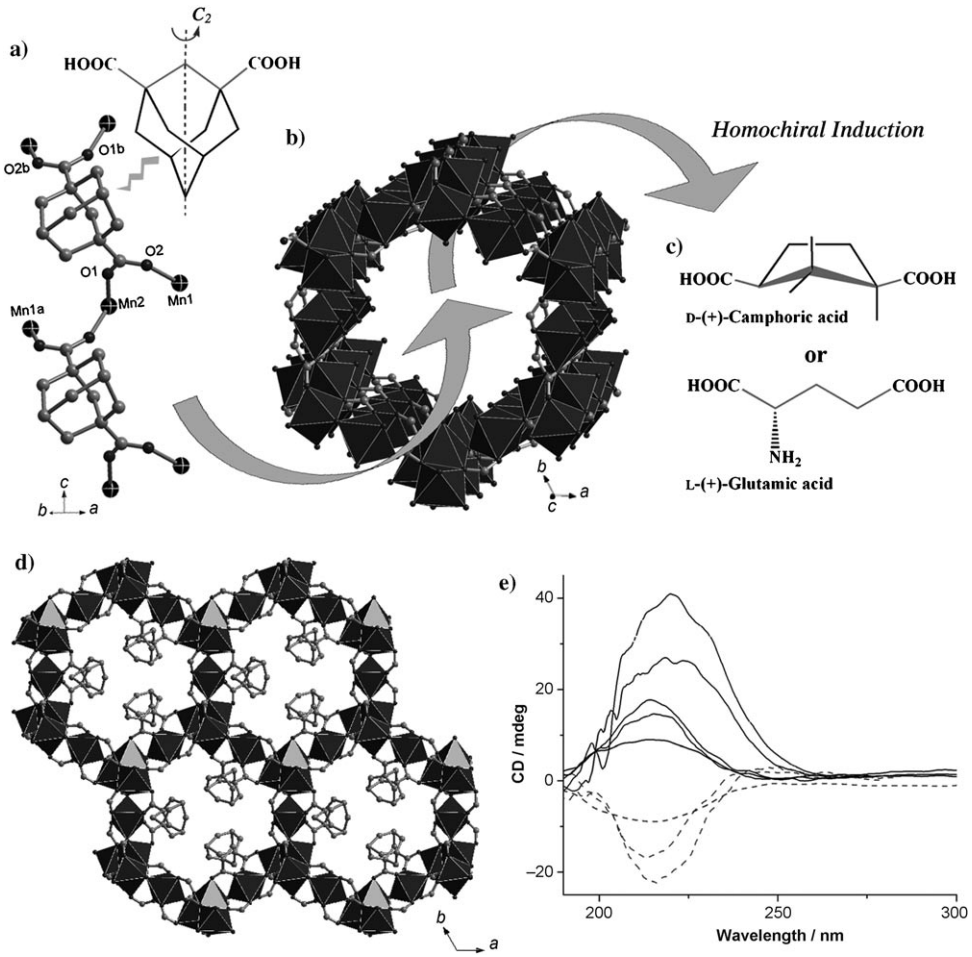


Figure 1. a) The $[Mn(adc)]_n$ chain based on achiral adc ligand with μ_4-coordination; b) the porous $[Mn_3(HCOO)_4]_n^{2+}$ channel based on inorganic Mn-O-Mn connectivity; c) two types of enantiopure catalysts used for synthesis and chiral induction of **1**D; The directions of arrows show the possible mechanism of chiral induction. D-camphoric acid initially controls the absolute chirality of $[Mn_3(HCOO)_4]_n^{2+}$ frameworks but is later displaced by adc. d) the 3D hybrid framework of **1**D, showing the achiral $[Mn(adc)]_n$ chains attached to the wall of the nanosized channels; e) the solid-state CD spectra of **1**D (——) and **1**L (-----). Each curve represents the signal from the sample of an independent synthesis.

crystal X-ray diffraction. The Flack parameter of each refinement indicates that 18 crystals belong to the $P3_221$ space group, while two crystals adopt the opposite $P3_121$ space group (Table S1 in the Supporting Information). This result suggests that when D-H_2cam is used as the additive, the product is enantioenriched with **1**D.

For the batch catalyzed with L-H_2cam, another set of twenty crystals was also randomly picked and analyzed using single-crystal X-ray diffraction. The Flack parameter of each refinement indicates that 18 crystals belong to the $P3_121$ space group, while two crystals adopt the opposite $P3_221$ space group (Table S2 in the Supporting Information). This result suggests that when L-H_2cam is used as the additive, the product is enantioenriched with **1**L.

Additional evidence for the asymmetric crystallization comes from solid-state circular dichroism (CD) spectroscopy. The CD spectra for the five batches catalyzed with D-H_2cam show that the bulk sample exhibits a positive CD signal at 218 nm (Figure 1e). In comparison, the CD spectra for the three batches catalyzed with L-H_2cam show that the bulk sample exhibits a negative CD signal at a similar wavelength (Figure 1e).

A comparative study of the four different crystallization processes (performed with D-, L-, or DL-H_2cam and without any H_2cam) not only further confirms the observed asymmetric crystallization but also offers insight into the mechanism of asymmetric crystallization (Scheme 1). When racemic DL-camphoric was used in place of enantiopure D- or L-H_2cam, the resulting bulk sample is a racemic conglomerate. With four randomly picked crystals, two belong to $P3_221$ and the other two belong to $P3_121$. Furthermore, no CD signal was detected for the bulk sample (Table S3 and Figure S3 in the Supporting Information).

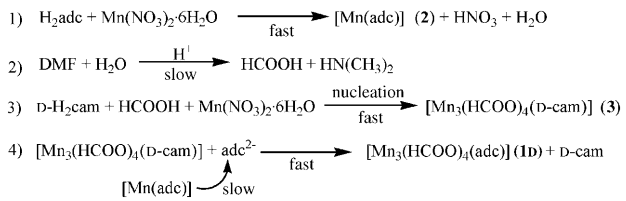
Interestingly, without the addition of H_2cam in any chiral form (D-, L-, or DL-), a new achiral layered compound [Mn(adc)] (**2**) was formed under otherwise identical reaction conditions. This finding demonstrates that the role of chiral H_2cam goes beyond just the control of the absolute chirality in the crystallization of **1**D or **1**L. Camphoric acid is in fact essential for growth of $[Mn_3(HCOO)_4(adc)]$ crystals.

The asymmetric crystallization of **1**D and **1**L is believed to result from cooperative interactions between chiral H_2cam and the achiral adc ligand. Because H_2cam has a similar coordination geometry to adc (in both, two COO^- groups are separated by three carbon atoms), the camphorate ligand is capable of directly participating in the nucleation and crystallization process, which allows the control of the absolute helicity of $[Mn_3(HCOO)_4]_n^{2n+}$ frameworks. However, adc ligands eventually replace the camphorate ligands in the final crystals.

The fact that the adc and camphorate ligands have similar binding features can be experimentally demonstrated. Indeed, without the competing adc ligand, camphoric acid can itself bind to the $[Mn_3(HCOO)_4]_n^{2n+}$ framework to directly control the absolute helicity of $[Mn_3(HCOO)_4]_n^{2n+}$, as evidenced by the reported isostructural crystals of homochiral $[Mn_3(HCOO)_4$(D-cam)] or $[Mn_3(HCOO)_4$(L-cam)].[15] When competing adc ligands are introduced, $[Mn_3(HCOO)_4$-(adc)] crystals are formed, and camphorate ligands can no longer be retained in the final crystals. Interestingly, despite being excluded from the final crystals, the camphorate ligand exhibits a chirality induction effect by controlling the absolute chirality of $[Mn_3(HCOO)_4(adc)]$ crystals. Thus the camphorate ligand controls the absolute chirality of the 3D porous $[Mn_3(HCOO)_4]^{2+}$ framework in two different ways (i.e., by direct binding to the framework or catalytic chiral induction, depending on whether the competing adc ligand is present or not).

To gain further insight into the crystallization process, time-dependent experiments were performed. When the clear solution of H_2adc, D-H_2cam, and $Mn(NO_3)_2{\cdot}3H_2O$ in DMF/ethanol (4:1) was heated at 120 °C for 3 h, a large amount of long needle-like crystals of achiral [Mn(adc)] (**2**) (yield 89 %) formed. In comparison, for the reaction examined after 12 h of heating, a small amount of hexagonal-prismatic crystals (**1**D) was also present together with crystals of achiral **2**, as confirmed by single-crystal X-ray diffraction. After four days, hexagonal-prismatic **1**D crystals were obtained in high yield (80 %). Because the needle-like crystals of achiral **2** can be washed away by ethanol, hexagonal-prismatic **1**D crystals can be easily separated. The chirality of the bulk sample was subsequently verified by CD spectra.

A four-step mechanism is shown in Scheme 2. The first step is the fast crystallization of achiral **2**. If the chiral induction agent (e.g., D-H_2cam) is not present, the process is over, and only achiral **2** is obtained, even after four days. The second step is the slow release of $HCOO^-$ from the decomposition of DMF, which is common in solvothermal synthesis. With the slow release of $HCOO^-$ from DMF, the homochiral nuclei of $[Mn_3(HCOO)_4$(D-cam)] (**3**) might be formed (the third step). While intermediate nuclei of **3** have not been directly detected, there are other experimental data to support the existence of this species. If the achiral adc ligand were not added, large crystals of **3** would form.[15] Finally, the chiral induction agent D-cam is replaced by the achiral adc ligand, which is the fourth step in the proposed mechanism.



Scheme 2. The four-step mechanism for the crystallization of homochiral **1**D. The achiral [Mn(adc)] (**2**) crystals are formed first in the initial hours and can persist for days in the absence of camphoric acid. However, in the presence of D-camphoric acid, the achiral [Mn(adc)] is converted into enantioenriched chiral $[Mn_3(HCOO)_4(adc)]$.

The gradual release of $HCOO^-$ anions from DMF is worth noting. The formate not only provides the necessary building units for **1**D, but it is closely associated with the kinetics of the crystallization process. However, the presence of too much formate all at once through the direct addition of HCOOH or

$HCOO^-$ at the beginning of the reaction led to the formation of manganese formate.

Recognizing the structural similarity between adc and camphorate ligands, we envisaged that other ligands with coordination geometry similar to H_2cam might also be able to function as the catalyst for the asymmetric crystallization of $[Mn_3(HCOO)_4(adc)]$. Indeed, the use of glutamic acid also leads to the asymmetric crystallization of $[Mn_3(HCOO)_4(adc)]$, as evidenced by the CD spectra (Figure S3 in the Supporting Information). However, unlike D- and L-camphoric acids, which give **1**D and **1**L, respectively, L-glutamic acid catalyzes the formation of **1**D, while D-glutamic acid catalyzes the formation of **1**L.

The above study with glutamic acid further suggests that to induce asymmetric crystallization, the chiral induction agent may need to possess proper coordination chemistry that matches well with the achiral framework building block. A similar example was recently found in the crystallization of a chiral zincophosphate.[16] To further investigate this idea, we also studied the effect of other amino acids (L-alanine, L-histidine, and L-aspartic acid) in the crystallization of $[Mn_3(HCOO)_4(adc)]$. For L-alanine, the achiral compound **2** was obtained, similar to the reaction performed without the use of any induction agent. For L-histidine, the resulting product is an unknown polycrystalline phase. For aspartic acid, neither achiral [Mn(adc)] nor chiral $[Mn_3(HCOO)_4(adc)]$ crystallized, and only aspartic acid crystals could be recovered.

In conclusion, we demonstrate herein an unusual asymmetric crystallization of a new 3D porous material constructed entirely from achiral building units by using enantiopure organic acids or amino acids as the chirality-inducing agents. In addition to controlling the absolute chirality, the chiral induction agent is also essential to initiate the nucleation of the chiral crystals. It is suggested that the chirality control is achieved through cooperative binding between enantiopure chiral reagents and achiral structural building units and that enantiopure chiral reagents control the absolute chirality of crystals by participating in the nucleation and crystallization processes but are later replaced with achiral ligands in the resulting crystals. The discovery that camphoric acid can control the absolute chirality of the 3D porous $[Mn_3(HCOO)_4]^{2+}$ framework by either direct binding to the framework or by catalytic chiral induction (depending on whether the competing adc ligand is present or not) is truly unprecedented and extraordinary.

Experimental Section

1D: Adamantane-1,3-dicarboxylic acid (H_2adc, 0.0798 g, 0.48 mmol), D-(+)-camphoric acid (0.0280 g, 0.13 mmol), and $Mn(NO_3)_2{\cdot}3H_2O$ (0.1390 g, 0.90 mmol) in DMF/ethanol (4.0415:0.8812 g) were placed in a 20 mL vial. The sample was heated at 120 °C for 4 days and then cooled to room temperature. After washing with ethanol, colorless crystals were obtained (yield: 80 %).

Crystal data for **1**D: $C_{16}H_{18}Mn_3O_{12}$, $M_r = 567.12$, trigonal, space group $P3_221$, $a = b = 15.1841(9)$, $c = 7.8474(9)$ Å, $V = 1566.9(2)$ Å^3, $Z = 3$, $\rho_{calcd} = 1.803$ g cm^{-3}, Flack parameter = 0.03(5), $R1(wR2) = 0.0510$ (0.1366) and $S = 1.099$ for 1602 reflections with $I > 2\sigma(I)$. Crystal data for **1**L: $C_{16}H_{18}Mn_3O_{12}$, $M_r = 567.12$, trigonal, space group $P3_121$, $a = b = 15.2162(10)$, $c = 7.9063(11)$ Å, $V = 1585.3(3)$ Å^3, $Z = 3$, $\rho_{calcd} = 1.782$ g cm^{-3}, Flack parameter = 0.00(4), $R1(wR2) = 0.0445$ (0.0944) and $S = 0.980$ for 1424 reflections with $I > 2\sigma(I)$. Crystal data for layered compound **2**: $C_{12}H_{14}MnO_4$, $M_r = 277.17$, monoclinic, space group Cc, $a = 7.7609(3)$, $b = 20.5827(9)$, $c = 7.0717(3)$ Å, $\beta = 93.411(3)°$, $V = 1127.63(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.633$ g cm^{-3}, Flack parameter = 0.59(3), $R1(wR2) = 0.0393$ (0.0759) and $S = 0.956$ for 1843 reflections with $I > 2\sigma(I)$.

CCDC 736430 (**1**D), 736431 (**1**L), and 736432 (**2**) 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.

Measurement of solid CD spectra: A mixture of about 3 mg sample and 40 mg dried KBr powder was well ground and then pressed into a disk for use in the CD measurements using a J-810 spectropolarimeter.

Received: November 5, 2009
Published online: January 14, 2010

Keywords: asymmetric amplification · chirality · homogeneous catalysis · metal–organic frameworks · microporous materials

[1] a) B. Kesanli, W. Lin, *Coord. Chem. Rev.* **2003**, *246*, 305; b) L. Ma, C. Abney, W. Lin, *Chem. Soc. Rev.* **2009**, *38*, 1248–1256.
[2] J. S. Seo, D. Whang, H. Lee, S. I. Jun, J. Oh, Y. J. Jeon, K. Kim, *Nature* **2000**, *404*, 982.
[3] a) G. Férey, *Chem. Soc. Rev.* **2008**, *37*, 191; b) J. Sun, C. Bonneau, Á. Cantín, A. Corma, M. J. Díaz-Cabañas, M. Moliner, D. Zhang, M. Li, X. Zou, *Nature* **2009**, *458*, 1154–1157; c) Y. Han, D. L. Zhang, L. L. Chng, J. L. Sun, L. Zhao, X. D. Zou, J. Y. Ying, *Nat. Chem.* **2009**, *1*, 123–127.
[4] A. J. Alexander, *Cryst. Growth Des.* **2008**, *8*, 2630.
[5] M. Lahav, L. Leiserowitz, *Cryst. Growth Des.* **2006**, *6*, 619.
[6] P. J. Walsh, M. C. Kozlowski, *Fundamentals of Asymmetric Catalysis*, University Science Books, Sausalito, California, **2009**.
[7] R. Vaidhyanathan, D. Bradshaw, J-N. Rebilly, J. P. Barrio, J. A. Gould, N. G. Berry, M. J. Rosseinsky, *Angew. Chem.* **2006**, *118*, 6645; *Angew. Chem. Int. Ed.* **2006**, *45*, 6495.
[8] D. N. Dybtsev, A. L. Nuzhdin, H. Chun, K. P. Bryliakov, E. P. Talsi, V. P. Fedin, K. Kim, *Angew. Chem.* **2006**, *118*, 930; *Angew. Chem. Int. Ed.* **2006**, *45*, 916.
[9] E. V. Anokhina, Y. B. Go, Y. Lee, T. Vogt, A. J. Jacobson, *J. Am. Chem. Soc.* **2006**, *128*, 9957.
[10] L. Pérez-García, D. B. Amabilino, *Chem. Soc. Rev.* **2002**, *31*, 342.
[11] a) D. K. Kondepudi, R. J. Kaufman, N. Singh, *Science* **1990**, *250*, 975; b) T. Ezuhara, K. Endo, Y. Aoyama, *J. Am. Chem. Soc.* **1999**, *121*, 3279; c) S. Wu, Y. Wu, Q. Kang, H. Zhang, L. Long, Z. Zheng, R. Huang, L. Zheng, *Angew. Chem.* **2007**, *119*, 8627; *Angew. Chem. Int. Ed.* **2007**, *46*, 8475; d) S. K. Tulashie, H. Lorenz, A. Seidel-Morgenstern, *Cryst. Growth Des.* **2009**, *9*, 2387.
[12] D. Bradshaw, T. J. Prior, E. J. Cussen, J. B. Claridge, M. J. Rosseinsky, *J. Am. Chem. Soc.* **2004**, *126*, 6106.
[13] Z. Lin, A. M. Z. Slawin, R. E. Morris, *J. Am. Chem. Soc.* **2007**, *129*, 4880.
[14] J. Zhang, S. Chen, T. Wu, P. Feng, X. Bu, *J. Am. Chem. Soc.* **2008**, *130*, 12882.
[15] J. Zhang, S. Chen, H. Valle, M. Wong, C. Austria, M. Cruz, X. Bu, *J. Am. Chem. Soc.* **2007**, *129*, 14168.
[16] J. Zhang, S. Chen, X. Bu, *Angew. Chem.* **2009**, *121*, 6165; *Angew. Chem. Int. Ed.* **2009**, *48*, 6049.

