[29] R. G. Raptis, H. H. Murray III, J. P. Fackler, Jr., *J. Chem. Soc. Chem. Commun.* **1987**, 737–739; H. H. Murray III, R. G. Raptis, J. P. Fackler, Jr., *Inorg. Chem.* **1988**, *27*, 26–31.

[30] From a formal point of view, also $NaCD_3$ (E. Weiss, S. Corbelin, J. K. Cockroft, A. N. Fitch, *Angew. Chem.* **1990**, *102*, 728–729; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 650–652; E. Weiss, S. Corbelin, J. K. Cockroft, A. N. Fitch, *Chem. Ber.* **1990**, *123*, 1629–1634) contains oligomers (in this case, tetramers) and polymeric chains. However, owing to a number of short intermolecular Na–C contacts between the two structural units, this distinction is not so evident.

[31] Indeed, a recent single-crystal structure determination performed in our laboratory on $[Ag(pyridazine)]NO_3$ has shown the copresence of dimers and 2_1-helical polymers: L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *Inorg. Chem.* **1998**, in press.

Combinatorial Material Libraries on the Microgram Scale with an Example of Hydrothermal Synthesis**

Jens Klein, Christian W. Lehmann, Hans-Werner Schmidt, and Wilhelm F. Maier*

Dedicated to Sir John Meurig Thomas on the occasion of his 65th birthday

As a consequence of the large number of possible polynary mixtures of oxidic materials, together with the potential use of many template molecules, it is attractive to apply combinatorial methods to hydrothermal synthesis.[1] While combinatorial methods are already established as important tools for the development of new lead structures in the areas of organic, biochemical, and pharmaceutical chemistry,[2] there are only a few examples known in the area of inorganic materials research or technical catalyst development. In particular the groups of P. G. Schultz and W. H. Weinberg have been actively involved since the mid 1990s in the development of combinatorial synthesis of new materials. These activities concentrated on the search of new compositions with superconducting,[3] magnetoresistant,[4] or luminescent[5] properties.

These applications are based on the deposition of the compounds as thin films through electron beam evaporation or RF sputtering. The library structure was obtained by the use of physical masks with lattice sizes between 100×100 and $200 \times 200\ \mu m^2$. Libraries with up to 25 000 different materials have been prepared and investigated by routine methods and new lead structures have already been "discovered".[3–5]

The most challenging problem is the analysis and characterization of the properties of interest. The amount of each sample is extremely small because of the miniaturized dimensions necessary for the generation of large libraries of materials. Akporiaye, Karlsson, and Wendelbo[6] published recently the application of combinatorial methods for hydrothermal synthesis. They developed an autoclave that allows 100 hydrothermal syntheses to be run in parallel at temperatures up to 200 °C. The phase diagram obtained in such a single experiment has been used to demonstrate the potential strengths of combinatorial approaches in the area of the synthesis of solid-state materials. In these experiments the reaction volumes were still in the range of 0.5 mL. The identification of the phases prepared still required manual removal of the solids from the reactors, followed by individual measurements with conventional X-ray diffraction techniques. The authors give no information on concentration and amounts of product actually achieved, but the amounts required were in the range of 1–10 mg. The sample handling after synthesis is still quite cumbersome. Every sample has to be prepared individually. Since we have been engaged for some time in the area of combinatorial methods for material synthesis, the above publication prompted us to present the results of our work.

The advantage of our reactor is the direct preparation of a library of materials, whose components can be identified automatically on the library substrate by X-ray microdiffraction. Another advantage is the reaction volume, which is smaller by a factor of 250 relative to that used in reference [6]. Figure 1 shows the construction with dimensions of the pressure reactor. For simplification the model shown has only 37 reaction chambers (each of diameter 1.4 mm and height 4 mm). There is no technical problem in reducing the size and

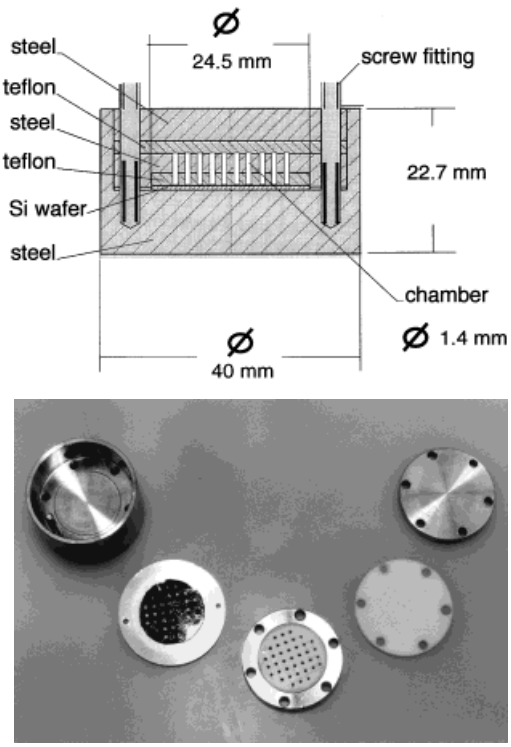

Figure 1. A cross-section of the multireactor autoclave (top) and a photograph of the individual reactor parts (bottom) with the orignial library on the Si wafer (second disk from the left).

[*] Prof. Dr. W. F. Maier, Dipl.-Chem. J. Klein, Dr. C. W. Lehmann, H.-W. Schmidt
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm Platz 1, D-45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2987
E-mail: maier@mpi-muelheim.mpg.de

[**] We thank the application laboratory of the Bruker AXS Company, Karlsruhe (Germany), especially A. Iberl for the use of their GADDS equipment and their support during the data collection. W.F.M. also thanks R. Boese for helpful discussions.

  1433-7851/98/3724-3369 $ 17.50+.50/0

increasing the number of the drilled holes to provide about 100 chambers on an area of about 4 cm^2. The bottom of the reactor is a Si wafer, the reactor walls (teflon disk with drilled holes) are pressed onto the Si disk by the steel disk that contains the same drilling pattern as the teflon disk. The reaction mixtures are dosed in amounts of up to 2 μL by a microliter pipette or a robot. The theoretical amounts of material obtainable range between 50 and 150 μg, the concentration of the reaction solutions are around 1 $\mu mol\,\mu L^{-1}$. By proper dilution of the reaction solution it can be assumed that the dosing of such small volumes is not affected by the viscosity. Once filled the reactor is sealed by a teflon disk, whose pressure can be adjusted by the top steel disk. This multichamber microautoclave is then brought to the reaction temperature required for hydrothermal synthesis conditions. After completion of the reaction the autoclave is cooled to room temperature and the reaction solution is separated from the solids formed by using small porous rods, with the solids remaining on the surface of the Si wafer. This procedure does by no means lead to quantitative recovery of the solid on the Si wafer, since together with some of the liquid some crystals will stick to the porous rod as well as to the inner teflon and steel walls of the reactor. However, quantitation is not the subject of this technique, since only a few crystals are required to obtain the desired diffraction pattern for identification. The product is washed several times with distilled water directly in the microreactors. The open autoclave is then heated to 100 °C to remove the remaining moisture. Thereafter, the Si wafer with the dried-on crystals can be removed and calcined at the desired temperature. During calcination the products sinter onto the Si wafer and the wafer then represents the library. The identification of the individual products can be carried out directly with a GADDS microdiffractometer from Bruker AXS. The powder diffractrograms are recorded with a 500 μm collimator that illuminates the whole spot area. The X-ray beam can be focussed maintaining high X-ray intensity by means of bent Göbel mirrors[8] to a diameter of 50 μm, whereby individual μm-sized particles become accessible to X-ray analysis. The library is mounted on the xyz stage of the diffractometer and the diffractograms are obtained in the reflection mode after the step parameters have been specified and the points to be measured identified. Because of the short sampling time required for each sample a large number of diffractrograms of individual spots as well as individual particles can be recorded overnight.

The practical application of such a combinatorial material synthesis has been investigated under hydrothermal conditions. The recipe for the preparation mixture of the well-known titanium-containing silicalite TS-1[7] was selected as the reference solution and the template molecules and metal components varied. The only information expected was "crystalline or amorphous" with a qualitative indication of the class of materials that had been formed. Figure 2 shows the actual library with the associated distances and spot identification codes. Each microreactor was filled with 2 μL of the individual reaction solutions. Table 1 summarizes the molar compositions of the various reaction mixtures. The reactor was sealed and treated as described above. The

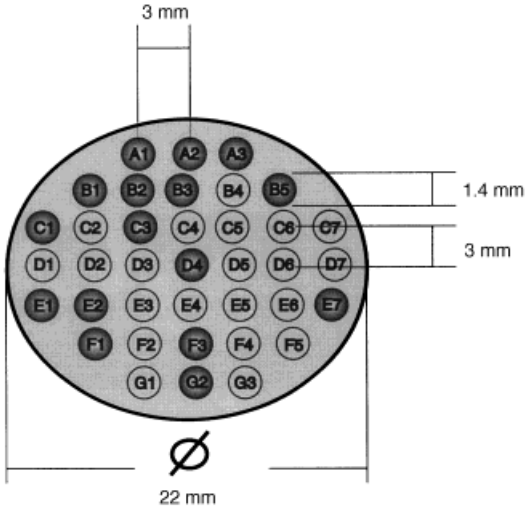

Figure 2. Identification plan of the library with the dimensions of the reactor chambers shown. The spots marked dark gray showed some crystallinity.

Table 1. Composition of the library shown in Figure 2.[a]

Chamber	Composition	Chamber	Composition
A1	Si:Ti:NPr_4OH 1:0.03:0.45	D5	Al:Ti:CTAB 1:0.05:0.1
A2	Si:Ti:NBu_4OH 1:0.03:0.45	D6	Al:Zr:NBu_4OH 1:0.2:0.4
A3	Si:Ti:NEt_4OH 1:0.03:0.45	D7	Al:Zr:NMe_4OH 1:0.2:0.4
B1	Si:Ti:NMe_4OH 1:0.03:0.45	E1	Al:Zr:NEt_4OH 1:0.2:1
B2	Si:Ti:C_4H_9N 1:0.03:0.45	E2	Al:Zr:CTAB 1:0.2:0.1
B3	Si:Ti:CTAB 1:0.03:0.045	E3	Ti:Zr:NBu_4OH 1:1:0.4
B4	Si:Ti:hexadecylamine 1:0.03:0.045	E4	Ti:Zr:NBu_4OH 1:1:0.4
B5	Si:Ti:hexadecylamine:NaOH 1:0.03:0.045:0.45	E5	Ti:Zr:NMe_4OH 1:1:0.4
C1	Si:Al:NPr_4OH 1:0.033:0.43	E6	Ti:Zr:NEt_4OH 1:1:1
C2	Si:Al:NPr_4OH 1:0.066:0.43	E7	Ti:Zr:CTAB 1:1:0.1
C3	Si:Zr:NPr_4OH 1:0.03:0.98	F1	Si:Ti:NPr_4OH 1:0.03:0.45
C4	Si:V:NPr_4OH 1:0.03:0.45	F2	Si:V:NPr_4OH 1:0.03:0.45
C5	Si:Zr:NBu_4OH 1:0.03:0.4	F3	Si:Ti:NEt_4OH 1:0.03:0.45
C6	Si:Zr:NMe_4OH 1:0.03:0.4	F4	Si:Zr:NPr_4OH 1:0.01:0.98
C7	Al:Ti:NBu_4OH 1:0.05:0.4	F5	Si:Al:NPr_4OH 1:0.1:0.43
D1	Al:Ti:NMe_4OH 1:0.05:0.4	G1	Si:Ti:NPr_4OH 1:0.03:0.45
D2	Al:Ti:NEt_4OH 1:0.05:1	G2	Al:Si:NPr_4OH 1:0.2:0.43
D3	Al:Ti:NEt_4OH 1:0.05:1	G3	Al:Si:NPr_4OH 1:0.1:0.43
D4	Al:Ti:CTAB 1:0.05:0.1		

[a] The molar ratio of the metal alkoxide (and also of the oxidized material in the product) and the templates are given under the composition. The sources for SiO_2, TiO_2, ZrO_2, and Al_2O_3 were tetraethoxysilane ($Si(OEt)_4$, TEOS), $Ti(OEt)_4$, $Ti(OiPr)_4$ or $Ti(OnPr)_4$, $Zr(OnPr)_4$ and $Al(OsBu)_3$. After removal of the alcohol from the externally prepared samples the reaction solutions were filled to 7.5 mL with distilled water, so that an excess of water was present for the hydrothermal synthesis of all samples (water:metal = 40:1).

  1433-7851/98/3724-3370 $ 17.50+.50/0

crystals formed on the Si wafer were then automatically characterized by X-ray diffraction studies.[9]

The dark dots in Figure 2 identify those positions containing crystalline materials. Figure 3 shows the amplified picture of one individual spot on the library surface. This photograph gives a good impression of the morphology of the materials assembled on the surface of the Si wafer. In the center of the

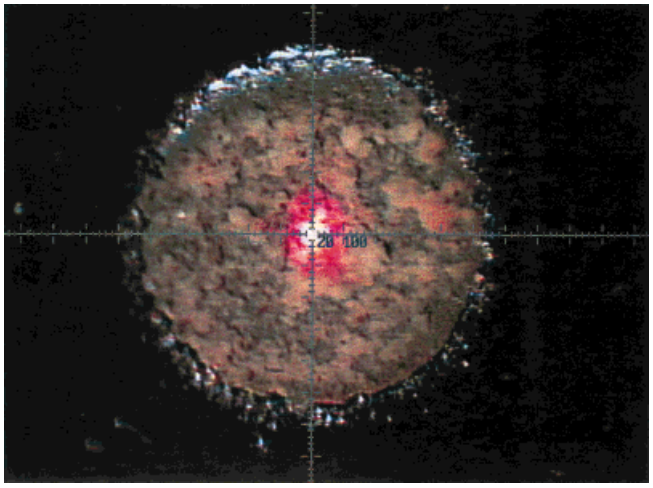

Figure 3. Photograph of the library spot B5 with the laser spot in the center (magnification 57).

cross-hairs a red laser spot can be identified, which is used to specify the position for the automated X-ray diffraction measurements. Figure 4 shows a typical X-ray image and the corresponding diffraction pattern obtained after integration,

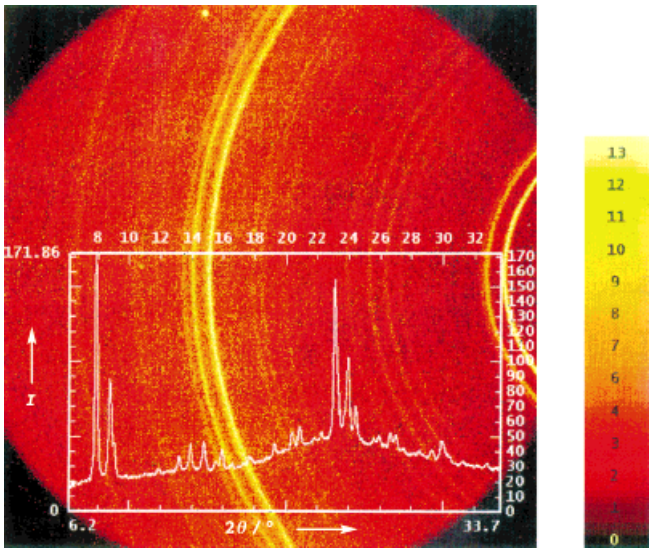

Figure 4. Typical diffraction pattern (number of faces) with the integrated reflection profile overlaid (point A1).

which is necessary to average particle and orientation effects that arise from the very small sample volume. Reflections from the library support were not brought into the diffracting position as a consequence of the selected measurement geometry.

Figure 5 shows the diffractograms of the two sample dots that contained the original synthesis solution for TS-1. Despite the small sample volume and the extremely small distances on the library an identical reproduction of the

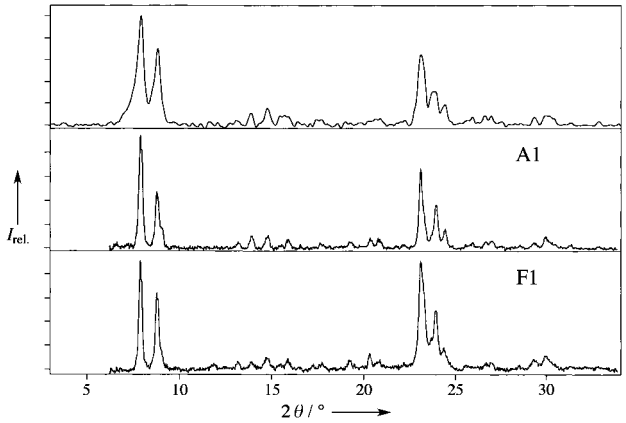

Figure 5. Comparison of the X-ray diffractogram from a conventionally obtained TS-1 sample (top) with the diffractograms from the library points A1 and F1 (middle and bottom, respectively).

original diffractogram[7] of TS-1 has been obtained, which confirms that zeolite synthesis on a microgram scale is possible and justified. Figure 6 displays selected diffractograms obtained from materials, which all show the MFI pattern typical for silicalites. This is not very surprising, since it is well-known that the identical structure of many Si-rich pentasil zeolites can be obtained with significantly different template molecules, such as diaminoalkanes, tetraalkylammonium, sols, or *n*-alkylamines.[10]

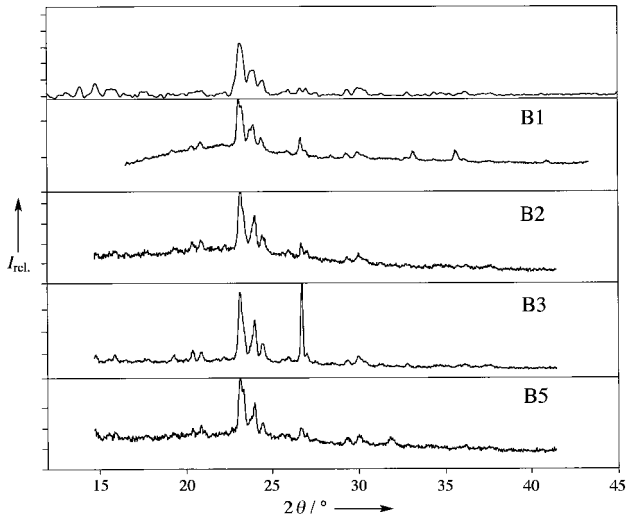

Figure 6. Diffractograms of the library points B1 – B5 showing the MFI structure typical for silicalites. The diffractogram of conventionally synthesized TS-1 is shown at the top.

Figures 3 – 6 show that by measurement over a larger 2θ area a complete phase identification is possible. Surprisingly, amorphous samples were also formed despite the pretreatment temperatures of 600 °C. The intensive powder line at

  1433-7851/98/3724-3371 $ 17.50+.50/0

26.65° of sample B3 is also consistant with the (101) reflection of quartz, and also with a preferred orientation of silicalite crystals. Under the reaction conditions used an oxidation of the Si-library substrate can be excluded, which is supported by the lack of such a reflection in the rest of the library. Examination of the dot areas after the experiment by light microscopy shows no signs of attack of the single crystal–wafer surface after removal of the crystal layers. For detailed characterization of the individual materials formed the interesting reactions identified by X-ray diffraction would have to be repeated and investigated by conventional means in the laboratory.

Our reaction system combined with analyses has an enormous potential for increased efficiency in the development of new materials and the automatization of characterization of samples obtained by combinatorial methods, and it is certainly not limited to the synthesis under hydrothermal conditions. Currently, the lower limit of 50 μm for the focussing of the X-ray beam restricts the miniaturization of the diameter of the microreactors. The material selected for the reactor walls limits reaction temperatures up to 300 °C; much higher temperatures may become possible through the selection of different polymeric materials. An increase in the library dimension to 10 cm diameter as well as a decrease in the drilling distance can readily be realized without technical problems.

Minimization of the manual efforts for the preparation of starting solutions as well as for the filling of the microreactors can be achieved readily with commercially available pipetting robots. Even the direct synthesis in the reactor by the direct use of ultrasound for proper mixing of the tiny probe volumes is realizable. In general, every solid synthesis in liquid phase under pressure and temperature should be possible. Such a reactor should be ideal for the combinatorial screening of new microcrystalline or amorphous solids, especially since the reactor bottom can be exchanged and libraries can be prepared directly on the substrate of choice.

Experimental Section

Our standard experimental conditions for the preparation of this material library have been described in the original literature of Taramasso et al.[7] Since only very small amounts are necessary to fill of the microreactors, the reaction volumes were reduced by a factor of 200 and mixed in 10-mL flasks. The reaction mixtures have been modified as described in Table 1. A1 and F1 each contain the original recipe as described in the patent.

The reaction was carried out in a sealed autoclave at a temperature of 200 °C for 36 h. After reaction the mother liquor was separated from the microreactor and the remaining crystals in the microreactor were washed several times with 2 μL of destilled water. The removal of the liquid was achieved by the capillary forces of porous rods directly in the microreactors. The compounds were then dried in the open microreactors at 100 °C. After removal of the teflon and steel mask the Si wafer with the dried-on crystal products were calcined at 600 °C for 10 h.

Received: April 30, 1998 [Z11806IE]
German version: *Angew. Chem.* **1998**, *110*, 3557–3561

Keywords: · combinatorial chemistry · hydrothermal synthesis · materials science · X-ray powder diffraction

[1] E. P. Feijen, J. A. Martens, P. A. Jacobs in *Studies in Surface Science and Catalysis*, *Vol. 84*, **1994**, pp. 3–21; A. Corma, *Chem. Rev.* **1997**, *97*, 2373–2419
[2] a) "Combinatorial Chemistry" *Acc. Chem. Res.* **1996**, *29* (special issue); b) G. Lowe, *Chem. Soc. Rev.* **1995**, *24*, 309–317; c) S. R. Wilson, A. W. Czarnik, *Combinatorial Chemistry—Synthesis and Application*, Wiley, **1997**
[3] X.-D. Xiang, X. Sun, G. Briceno, Y. Lou, K.-A. Wang, H. Chang, W. G. Wallace-Freedman, S.-W. Chen, P. G. Schultz, *Science* **1995**, *268*, 1738–1740
[4] G. Briceno, H. Chang, X. Sun, P. G. Schultz, X.-D. Xiang, *Science* **1995**, *270*, 273–275)
[5] a) E. Danielson, J. H. Golden, E. W. McFarland, C. M. Reaves, W. H. Weinberg, X. D. Wu, *Nature* **1997**, *389*, 944–948; b) E. Danielson, M. Devenney, D. M. Giaquinta, J. H. Golden, R. C. Haushalter, E. W. McFarland, D. M. Poojary, C. M. Reaves, W. H. Weinberg, X. D. Wu, *Science* **1998**, *279*, 837–839
[6] a) D. E. Akporiaye, I. M. Dahl, A. Karlsson, R. Wendelbo, *Angew. Chem.* **1998**, 110, 629; *Angew. Chem. Int. Ed.* **1998**, *37*, 609; b) D. E. Akporiaye, I. M. Dahl, A. Karlsson, R. Wendelbo, patent pending, Norwegian application number 97.0788
[7] M. Taramasso, G. Perego, B. Notari (Snamprogetti), UK-GB, 2071071 B **1979**.
[8] M. Schuster, H. Göbel, *J. Phys. D* **1995**, *28*, A270–A275.
[9] All diffraction data were measured with $Cu_{K\alpha}$ radiation ($\lambda = 1.541$ Å). Data collection time varied from 5 to 80 min per spot. The distance between the sample and detector was 19.8 cm and the range between 6.2 and 33.2° (2θ). During data collection the sample oscillated by 2° and with an incident angle of the primary X-ray beam of 16°. The spatially corrected raw data have been integrated with a constant 2θ value (Laue cones).
[10] B. M. Lok, T. R. Cannan, C. A. Messina, *Zeolites* **1983**, *3*, 282–291.

Chiral C_2-Symmetric Cu^{II} Complexes as Catalysts for Enantioselective Hetero-Diels–Alder Reactions**

David A. Evans,* Edward J. Olhava, Jeffrey S. Johnson, and Jacob M. Janey

Previous reports from this laboratory have demonstrated that C_2-symmetric Cu^{II}–bis(oxazoline) complexes **1**–**3**[1] (Tf = trifluoromethanesulfanyl) are efficient chiral Lewis acid catalysts for Diels–Alder,[2] pyruvate aldol,[3] and glyoxylate–ene reactions.[4] Each of these processes exhibits behavior consistent with previously proposed chelation models for asymmetric induction. In a further extension of this methodology, we recently reported that α,β-unsaturated acyl phosphonates undergo enantioselective hetero-Diels–Alder

[*] Prof. D. A. Evans, E. J. Olhava, J. S. Johnson, J. M. Janey
Department of Chemistry & Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-1460
E-mail: evans@chemistry.harvard.edu

[**] Financial support has been provided by the National Science Foundation. E.J.O. acknowledges a National Science Foundation Graduate Fellowship. J.S.J. acknowledges a Pharmacia and Upjohn Graduate Fellowship. The National Institutes of Health (BRS Shared Instrumentation Grant Program 1-S10-RR04870) and the NSF (CHE 88–14019) are acknowledged for providing NMR facilities.

  1433-7851/98/3724-3372 $ 17.50+.50/0