compounds, cells resumed migration and proliferated to give a confluent layer, indicating the drugs were not cytotoxic over the time course of this assay.

This example establishes that the dynamic substrates are compatible with experiments to modulate cell behavior in situ and in real time. Our results suggest that this method will be broadly useful in assays for screening libraries of drug candidates that have antimigratory effects, and that can block metastasis in cancer.[16] These substrates also offer immediate opportunities for mechanistic studies of cell migration including investigations of the dependence of cell migration on the density and affinity of immobilized ligands. Finally, these active surfaces can be combined with microelectrode arrays to modulate the presentation of ligands on select regions of the substrate and to even immobilize multiple ligands on the substrate.

The most important feature of this method is that these substrates are defined at the molecular scale and therefore provide complete control over ligand–receptor interactions between cell and substrate. The use of physical organic and synthetic chemistry was critical to the design and preparation of this dynamic substrate. This molecular approach is significant because it can be applied to the design of dynamic substrates having other functions, including those that selectively release immobilized ligands and that reversibly modulate the activities of ligands.[17] Most importantly, the chemical approach described here provides unprecedented control in developing tailored substrates for modulating cell behavior, and will have an impact on programs in bioorganic chemistry, cell biology, and materials science.

Received: September 21, 2000 [Z15840]

[1] a) R. O. Hynes, *Cell* **1992**, *69*, 11; b) J. C. Adams, F. M. Watt, *Development* **1993**, *117*, 1183; c) E. A. Clark, J. S. Brugge, *Science* **1995**, *268*, 233; d) M. A. Schwartz, M. D. Schaller, M. H. Ginsberg, *Annu. Rev. Cell Dev. Biol.* **1995**, *11*, 549.

[2] P. Friedl, E. B. Brocker, *Cell Mol. Life Sci.* **2000**, *57*, 41.

[3] SAMs are currently the best available class of model substrates for studies in biointerfacial science. For reviews, see M. Mrksich, *Chem. Soc. Rev.* **2000**, *29*, 267.

[4] (1-Mercapto-undec-11-yl)penta(ethlyene glycol) was prepared as described by C. Pale-Grosdemange, E. S. Simon, K. L. Prime, G. M. Whitesides, *J. Am. Chem. Soc.* **1991**, *113*, 12. The hydroquinone alkanethiol conjugate was prepared in seven steps from 2,5-dimethoxybromobenzene (Aldrich) and (1-mercapto-undec-11-yl)tetra(ethylene glycol). Peptides were synthesized on Fmoc-Rink amide MHBA resin (Anaspec) using standard protocols. The Arg-Gly-Asp cyclopentadiene conjugate Gly-Arg-Gly-Asp-Ser-NH_2 was prepared in two steps from cyclopenta-1,3-dienylacetic acid and Abu-Arg-Gly-Asp-Ser-NH_2.

[5] a) M. N. Yousaf, E. W. L. Chan, M. Mrksich, *Angew. Chem.* **2000**, *112*, 2016; *Angew. Chem. Int. Ed.* **2000**, *39*, 1943; b) E. W. L. Chan, M. N. Yousaf, M. Mrksich, *J. Phys. Chem. A* **2000**, *104*, 9315.

[6] M. N. Yousaf, M. Mrksich, *J. Am. Chem. Soc.* **1999**, *121*, 4286.

[7] M. Mrksich, G. M. Whitesides, *ACS Symp. Ser.* **1997**, *680*, 361.

[8] Cyclic voltammetry was performed with a Bioanalytical Systems CV-50 potentiostat using a cell with the gold/SAM as the working electrode, platinum wire as the counter electrode, and Ag/AgCl as the reference electrode.

[9] E. Ruoslahti, *Annu. Rev. Cell Dev. Biol.* **1996**, *12*, 697.

[10] a) C. Roberts, C. S. Chen, M. Mrksich, V. Martinchonok, D. E. Ingber, G. M. Whitesides, *J. Am. Chem. Soc.* **1998**, *120*, 6548; b) B. T. Houseman, M. Mrksich, *J. Org. Chem.* **1998**, *63*, 7552; c) B. T. Houseman, M. Mrksich, *Biomaterials*, in press.

[11] Swiss Albino 3T3 cells (ATCC) were cultured in Dulbecco's Modified Eagle Medium (Gibco) supplemented with 10% fetal bovine serum and penicillin/streptomycin. Cells were removed with a solution of 0.05% trypsin/0.53 mM ethylendiaminetetraacetate (EDTA), resuspended in serum-free culture medium (60000 cells mL^{-1}), and plated onto the SAM substrates. After four hours the serum-free medium was replaced with medium containing serum.

[12] Patterned substrates containing islands coated with fibronectin were prepared using microcontact printing.[13] Hexadecanethiol [$HS(CH_2)_{15}CH_3$] was printed onto gold-coated substrates with a poly(dimethylsiloxane) stamp containing the pattern in relief. The substrate was then immersed immediately in an ethanolic solution containing the quinone alkanethiol conjugate and (1-mercapto-undec-11-yl)penta(ethylene glycol) (10 μM in quinone, 1 mM in total thiol), which modified the remaining bare regions of gold with monolayer. The substrates were immersed in a solution of fibronectin (100 μg mL^{-1} in phosphate-buffered saline) for four hours, to modify only the stamped regions with an adsorbed layer of protein.

[13] a) R. Singhvi, A. Kumar, G. P. Lopez, G. N. Stephanopoulas, D. I. C. Wang, G. M. Whitesides, D. E. Ingber, *Science* **1994**, *264*, 696; b) C. S. Chen, M. Mrksich, S. Huang, G. M. Whitesides, D. E. Ingber, *Science* **1997**, *276*, 1425.

[14] This concentration of RGD-Cp permitted efficient immobilization of the peptide but did not interfere with the adhesion of cells confined to the patterned regions of fibronectin.

[15] Serum-free culture medium containing soluble RGD peptide (2 mM) removed cells from regions presenting immobilized peptide but had no effect on cells attached to regions coated with fibronectin. When the medium was exchanged to remove the soluble peptide, cells again migrated and proliferated to give a confluent layer.

[16] a) W. L. Rust, J. L. Huff, G. E. Plopper, *Anal. Biochem.* **2000**, *280*, 11; b) R. Kapur, K. A. Giuliano, M. Campana, T. Adams, K. Olson, D. Jung, M. Mrksich, C. Vasudevan, D. L. Taylor, *Biomed. Microdev.* **1999**, *2*, 99.

[17] C. D. Hodneland, M. Mrksich, *J. Am. Chem. Soc.* **2000**, *122*, 4235.

Asymmetric Induction by Helical Hydrocarbons: [6]- and [5]Helicenes**

Itaru Sato, Ryutaro Yamashima, Kousuke Kadowaki, Jun Yamamoto, Takanori Shibata, and Kenso Soai*

Enantiomerically enriched organic compounds that have been used as chiral catalysts and ligands in asymmetric synthesis possess a heteroatom(s) such as oxygen, nitrogen, sulfur, and phosphorus in addition to carbon and hydrogen atom(s).[1] To the best of our knowledge, no chiral hydrocarbon has ever been used successfully as a chiral ligand or catalyst in asymmetric synthesis. On the other hand, [6]- and

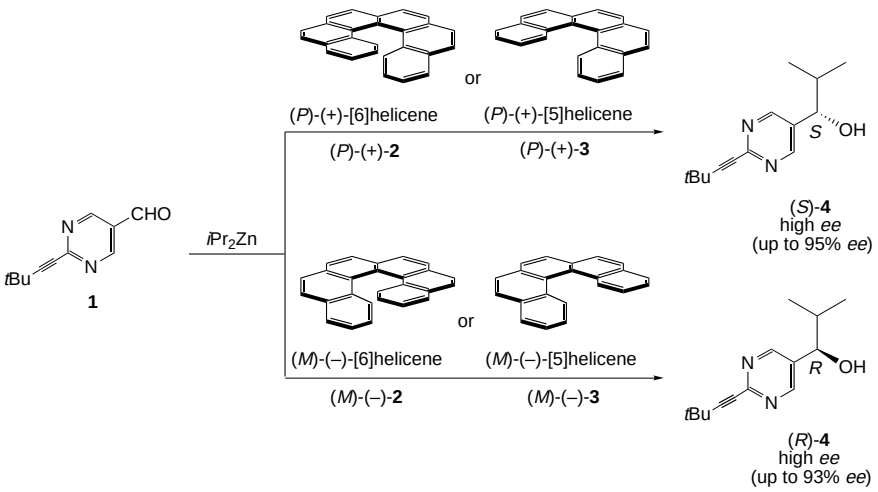
[*] Prof. Dr. K. Soai, Dr. I. Sato, R. Yamashima, K. Kadowaki, J. Yamamoto, Dr. T. Shibata
Department of Applied Chemistry, Faculty of Science
Science University of Tokyo
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)
Fax: (+81) 3-3235-2214
E-mail: ksoai@ch.kagu.sut.ac.jp

[**] This work was generously supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, and by the Japan Space Forum. I.S. is grateful for a Daicel Award for Synthetic Organic Chemistry, Japan.

  1433-7851/01/4006-1096 $ 17.50+.50/0

[5]helicene are hydrocarbons with chiral helical structures.[2] However, helicene skeletons have rarely been used in enantioselective synthesis. Chiral phosphane ligands with helicene skeletons,[3] and a chiral diol with a bis[5]helicene skeleton[4] have been prepared and were used as a chiral ligand[3a] and as a catalyst,[4] respectively. In these cases, coordination of the phosphorus and oxygen atoms with metals is considered to play an essential role in the induction of asymmetry. It has thus been a challenge to induce asymmetry in enantioselective syntheses using helical hydrocarbons without any heteroatoms.

We report herein that chiral [6]- and [5]helicene act as chiral inducers in the highly enantioselective synthesis of a pyrimidyl alkanol by the enantioselective addition of diisopropylzinc (iPr$_2$Zn) to 2-(2-*tert*-butylethynyl)pyrimidine-5-carbaldehyde (**1**; Scheme 1, Table 1). When aldehyde **1** (0.05 mmol)[5] was treated with iPr$_2$Zn (0.15 mmol)[6] in the presence of (*P*)-(+)-[6]helicene ((*P*)-(+)-**2**; 6 mol%, >99.5% *ee*[7]) at 0 °C in toluene, and aldehyde **1** and iPr$_2$Zn were successively added in two portions (0.2 and 0.8 mmol of aldehyde **1**, 0.48 and 1.92 mmol of iPr$_2$Zn, respectively), (*S*)-5-pyrimidyl alkanol (*S*)-**4** was obtained (95% *ee*, 95% yield) (Table 1, entry 1). On the other hand, in the presence of (*M*)-(−)-**2** (7 mol%), the opposite enantiomer (*R*)-**4** was formed (93% *ee*, 93% yield) (Table 1, entry 2). The sense of the asymmetric induction, in which [6]helicene (*P*)-(+)-**2** gives (*S*)-**4** and [6]helicene (*M*)-(−)-**2** gives (*R*)-**4**, is also the case with [5]helicene **3**.[8] Thus, in the same way, the asymmetric addition of iPr$_2$Zn in the presence of (*P*)-(+)-**3** (11 mol%, 64% *ee*) gave (*S*)-**4** (95% *ee*, 88% yield) (Scheme 1; Table 1, entry 3), whereas in the presence of (*M*)-(−)-**3** (11 mol%, 60% *ee*), the reaction gave (*R*)-**4** (94% *ee*, 89% yield) (Table 1, entry 4). These high *ee* values and the absolute configurations of **4** may be rationalized as follows: 1) [6]- and [5]helicenes without any heteroatoms induce asymmetry in the initially formed zinc alkoxide of **4**, with the absolute configuration regulated by the *P* or *M* helicity of helicenes, and 2) asymmetric autocatalysis[5, 9] of the zinc alkoxide of **4** with an amplification of *ee* affords alkanol **4** with very high *ee*.[10, 11]



Scheme 1. Enantioselective synthesis of **4** in the presence of [6]- and [5]helicenes.

Table 1. Enantioselective synthesis of **4** in the presence of [6]- and [5]helicenes.

Entry	Helicene		Method[a]	Alkanol **4**[b]		
	ee [%]	mol%		Config.	Yield [%]	*ee* [%]
1	(*P*)-(+)-**2**	>99.5	6.2	A	*S*	95	95
2	(*M*)-(−)-**2**	>99.5	7.0	A	*R*	93	93
3	(*P*)-(+)-**3**	67	11	A	*S*	88	95
4	(*M*)-(−)-**3**	60	11	A	*R*	89	94
5	(*P*)-(+)-**2**	≈0.13	11	B	*S*	88	56
6	(*M*)-(−)-**2**	≈0.54	9.8	B	*R*	92	62

[a] Reactions were carried out in toluene at 0 °C. Method A: Aldehyde **1** and iPr$_2$Zn were added in two portions. Method B: Aldehyde **1** and iPr$_2$Zn were added in three portions. [b] The *ee* value was determined by HPLC analysis on a column fitted with a chiral stationary phase.

More significantly, (*P*)- and (*M*)-[6]helicenes with *ee* values as low as approximately 0.13% and 0.54% act as chiral inducers to afford (*S*)- and (*R*)-**4** with *ee* values of 56% and 62%, respectively (Table 1, entries 5 and 6). These moderate enantiomeric excesses can be considerably amplified by the consecutive asymmetric autocatalysis of **4**.[9f]

[6]Helicene has been shown to form a diastereomeric charge-transfer complex with an enantiomer of a chiral aromatic compound with electron-withdrawing groups.[12] In the present case, we postulate an interaction between [6]helicene and aldehyde **1** based on the calculated formaldehyde–benzene[13] interactions and on the following ^{1}H NMR spectroscopy (300 MHz) results: the time-averaged chemical shifts measured from a solution of **1** in $CDCl_3$ (0.031M) shifted upfield upon the addition of [6]helicene. This shift showed an almost linear correlation with the addition of [6]helicene from 0 to 6.3 mol equivalents. Notably, the $\Delta\delta$ values of the signals for the aldehyde proton and for the protons of the pyrimidine ring are larger (−13.3 Hz and −9.1 Hz, respectively, per molar equivalent of [6]helicene)[14] than those of the protons on the *tert*-butyl group (−1.1 Hz). This suggests a coordination of the [6]helicene with the carbonyl moiety and the pyrimidine ring of aldehyde **1**. When chiral [6]helicene coordinates with aldehyde **1**, it may differentiate between the *Re* and *Si* face of aldehyde **1**. When iPr$_2$Zn is added to aldehyde **1**, a nonracemic zinc alkoxide of alkanol **4** is considered to be formed initially.

In summary, we have described for the first time a highly enantioselective synthesis induced by chiral helical hydrocarbons. It should be emphasized that our present results formally correlate the chirality of circularly polarized light (CPL) and the chirality of an organic compound with high *ee* because [6]helicene is a well-accepted substrate that is enantioselectively (<2% *ee*) synthesized by CPL.[11, 15]

  1433-7851/01/4006-1097 $ 17.50+.50/0

Experimental Section

The alkylation in the presence of (*P*)-(+)-**2** with ≈0.13 % *ee* is representative (Table 1, entry 5). The *ee* value of **2** was determined by comparison of its specific rotation ($[\alpha]_D^{28} = +4.8^\circ$ ($c = 1.68$, $CHCl_3$)) with that of an enantiomerically pure sample (lit. [16] $[\alpha]_D^{20} = +3707^\circ$ ($c = 0.082$, $CHCl_3$)). A solution of $i Pr_2Zn$ in toluene (1M, 0.15 mL) was added dropwise over a period of 30 min at 0 °C to a solution of aldehyde **1** (9.4 mg, 0.05 mmol) and (*P*)-(+)-**2** (36.9 mg, 0.11 mmol) in toluene (2.5 mL). After the mixture was stirred for 16 h, toluene (0.8 mL), a solution of $i Pr_2Zn$ in toluene (1M, 0.48 mL), and aldehyde **1** (37.6 mg, 0.2 mmol) in toluene (1.5 mL) were added successively. After 7 h, toluene (4.7 mL), a solution of $i Pr_2Zn$ in toluene (1M, 1.92 mL), and aldehyde **1** (151 mg, 0.8 mmol) in toluene (2 mL) were added, and the mixture was stirred for an additional 16 h. The reaction was quenched by the addition of hydrochloric acid (1M, 5 mL), and made alkaline by the addition of saturated aqueous sodium bicarbonate (15 mL). The mixture was filtered through celite, and the separated aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Purification of the residue by thin-layer chromatography on silica gel (developing solvent: hexane/ethyl acetate 2:1) gave pyrimidyl alkanol **4** (215 mg, 88 %). The *ee* value was determined to be 56 % by HPLC analysis using a chiral stationary phase (Daicel Chiralcel OD).

Received: November 20, 2000 [Z16142]

[1] a) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; b) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley, New York, **2000**.

[2] a) R. H. Martin, *Angew. Chem.* **1974**, *86*, 727 – 738; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 649 – 660; b) R. H. Janke, G. Haufe, E.-U. Würthwein, J. H. Borkent, *J. Am. Chem. Soc.* **1996**, *118*, 6031 – 6035; c) S. Grimme, S. D. Peyerimhoff, *Chem. Phys.* **1996**, *204*, 411 – 417; d) J. M. Schulman, R. L. Disch, *J. Phys. Chem. A* **1999**, *103*, 6669 – 6672.

[3] a) M. T. Reetz, E. W. Beuttenmüller, R. Goddard, *Tetrahedron Lett.* **1997**, *38*, 3211 – 3214; b) A. Terfort, H. Görls, H. Brunner, *Synthesis* **1997**, 79 – 86.

[4] S. D. Dreher, T. J. Katz, K. C. Lam, A. L. Rheingold, *J. Org. Chem.* **2000**, *65*, 815 – 822.

[5] T. Shibata, S. Yonekubo, K. Soai, *Angew. Chem.* **1999**, *111*, 749 – 751; *Angew. Chem. Int. Ed.* **1999**, *38*, 659 – 661.

[6] For a review, see: K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833 – 856.

[7] Racemic [6]helicene (R. H. Martin, M.-J. Marchant, M. Baes, *Helv. Chim. Acta* **1971**, *54*, 358 – 360) was resolved by preparative HPLC using a chiral stationary phase (Chiralcel OD).

[8] Racemic [5]helicene (F. Dubois, M. Gingras, *Tetrahedron Lett.* **1998**, *39*, 5039 – 5040) was resolved by preparative HPLC using a chiral stationary phase (Chiralcel OD).

[9] a) K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767 – 768; b) T. Shibata, H. Morioka, T. Hayase, K. Choji, K. Soai, *J. Am. Chem. Soc.* **1996**, *118*, 471 – 472; c) T. Shibata, J. Yamamoto, N. Matsumoto, S. Yonekubo, S. Osanai, K. Soai, *J. Am. Chem. Soc.* **1998**, *120*, 12157 – 12158; d) K. Soai, S. Osanai, K. Kadowaki, S. Yonekubo, T. Shibata, I. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 11235 – 11236; e) I. Sato, K. Kadowaki, K. Soai, *Angew. Chem.* **2000**, *112*, 1570 – 1572; *Angew. Chem. Int. Ed.* **2000**, *39*, 1510 – 1512; f) K. Soai, T. Shibata, I. Sato, *Acc. Chem. Res.* **2000**, *33*, 382 – 390.

[10] For reviews on asymmetric autocatalysis with amplification of *ee*, see: a) K. Soai, *Enantiomer* **1999**, *4*, 591 – 598; b) K. Soai, T. Shibata, *Yuki Gosei Kagaku Kyokaishi* **1997**, *55*, 994 – 1005; c) H. Buschmann, R. Thede, D. Heller, *Angew. Chem.* **2000**, *112*, 4197 – 4199; *Angew. Chem. Int. Ed.* **2000**, *39*, 4033 – 4036; d) C. Bolm, F. Bienewald, A. Seger, *Angew. Chem.* **1996**, *108*, 1767 – 1769; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1657 – 1659; e) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Chem. Commun.* **2000**, 887 – 892; for reviews of non-autocatalytic and autocatalytic reactions with amplification of *ee*, see: f) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088 – 3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922 – 2959; g) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki, R. Angelaud, *Angew. Chem.* **2000**, *112*, 3676 – 3701; *Angew. Chem. Int. Ed.* **2000**, *39*, 3532 – 3557; h) K. Soai, T. Shibata in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 699 – 725.

[11] For a review, see: B. L. Feringa, R. A. van Delden, *Angew. Chem.* **1999**, *111*, 3624 – 3645; *Angew. Chem. Int. Ed.* **1999**, *38*, 3418 – 3438.

[12] J. M. Brown, I. P. Field, P. J. Sidebottom, *Tetrahedron Lett.* **1981**, *22*, 4867 – 4870.

[13] H. Ihara, T. Sagawa, K. Nakashima, K. Mitsuishi, Y. Goto, J. Chowdhury, S. Sakaki, *Chem. Lett.* **2000**, 128 – 129.

[14] When benzene was added to a solution of **1** in $CDCl_3$ (0.031M), the $\Delta\delta$ values of the signals for the aldehyde proton and for the protons of the pyrimidine ring are −1.5 Hz and −0.9 Hz, respectively, per molar equivalent of benzene.

[15] a) A. Moradpour, J. F. Nicoud, G. Balavoine, H. B. Kagan, G. Tsoucaris, *J. Am. Chem. Soc.* **1971**, *93*, 2353 – 2354; b) W. J. Bernstein, M. Calvin, O. Buchardt, *J. Am. Chem. Soc.* **1972**, *94*, 494 – 497; for a review, see: Y. Inoue, *Chem. Rev.* **1992**, *92*, 741 – 770.

[16] *Dictionary of Organic Compounds* (Ed.: J. Buckingham), 5th ed., Chapman and Hall, New York, **1983**.

Interprotein Electron Transfer Reaction Regulated by an Artificial Interface**

Yutaka Hitomi, Takashi Hayashi,* Kenji Wada, Tadashi Mizutani, Yoshio Hisaeda, and Hisanobu Ogoshi

Electron transfer (ET) reactions are fundamental to numerous important biological processes such as respiration, photosynthesis, and redox reactions of intermediary metabolism. In these systems, interprotein ET reactions are regulated by a specific interaction between two redox proteins. A unique charge distribution on the protein surface is responsible for this recognition. For example, cytochrome *c*, an electron carrier between complexes III and IV of the respiratory chain, has several highly conserved lysine residues surrounding the slightly exposed heme edge, while redox partners have a recognition domain consisting of anionic residues with the same topological symmetry as the lysine

[*] Prof. Dr. T. Hayashi, Prof. Dr. Y. Hisaeda
Department of Synthetic Chemistry and Biochemistry
Graduate School of Engineering, Kyushu University
Fukuoka 812-8581 (Japan)
Fax: (+81) 92-632-4718
E-mail: thayatcm@mbox.nc.kyushu-u.ac.jp
Dr. Y. Hitomi, K. Wada, Prof. Dr. T. Mizutani
Department of Synthetic Chemistry and Biological Chemistry
Graduate School of Engineering, Kyoto University
Kyoto 606-8501 (Japan)
Prof. Dr. H. Ogoshi
Fukui National College of Technology
Sabae, Fukui 916-8507 (Japan)

[**] We thank Prof. Dr. I. Morishima and his group for the arrangement of laser flash photolysis equipment. This work was supported by Nagase Science and Technology Foundation, and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan. Y. H. was supported by Research Fellowships of the Japanese Society for the Promotion of Science for Young Scientists.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  1433-7851/01/4006-1098 $ 17.50+.50/0