Fluorescent Sensors

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Highly Enantioselective Recognition of Structurally Diverse α-Hydroxycarboxylic Acids using a Fluorescent Sensor**

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The rapid construction of libraries of chiral organic compounds in drug discovery and the efforts to develop high-throughput chiral-catalyst screening techniques demand rapid and sensitive analytical tools for chiral assays. Amongst many of the enantioselective methods under investigation,[1–4] the use of fluorescence has attracted a sizable interest because it can offer the advantages of real-time analysis, high sensitivity, multiple sensing modes, widely available instrumentation, and remote detection capabilities.[3,4] During the past several years, there has been a growing interest in the enantioselective recognition of α-hydroxycarboxylic acids,[5–8] especially using fluorescence spectroscopy,[7,8] owing to the synthetic utility of this class of molecules and their biological significance. Several fluorescent sensors, including those developed within our group, have been reported to show high enantioselectivity in the recognition of mandelic acid and/or hexahydromandelic acid.[7] However, the enantioselective recognition of other chiral α-hydroxycarboxylic acids is poor, and the normalized ratios of the fluorescence intensity of the sensors when treated with the two enantiomers of these acid substrates, that is I_R/I_S or I_S/I_R, are all less than 2.[4f,8] Therefore, the development of enantioselective fluorescent sensors for structurally diverse α-hydroxycarboxylic acids has become a major challenge in this area.

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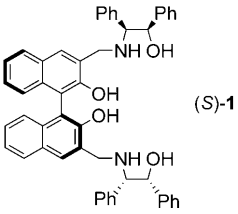
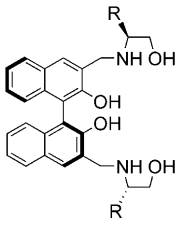
Recently, we reported the use of 1,1′-bi-2-naphthol(BINOL)-amino alcohol molecule (*S*)-**1** for the recognition of mandelic acid.[7e] When (*S*)-**1** was treated with (*S*)-mandelic acid, a white precipitate was formed. This precipitate, a complex between (*S*)-**1** and four molecules of (*S*)-mandelic acid, showed a large solid state fluorescence enhancement. In contrast, when (*S*)-**1** was treated with (*R*)-mandelic acid, no precipitate was generated and little fluorescence enhancement was observed. (*S*)-**1** can be used as an enantioselective sensor for the recognition of mandelic acid and hexahydromandelic acid; however, the enantioselective fluorescent response of (*S*)-**1** toward other α-hydroxycarboxylic acids was low. To improve the scope of (*S*)-**1** for the enantioselective fluorescent recognition of α-hydroxycarboxylic acids, we conducted a systematic modification of the structure of this compound. Herein, we report an enantioselective fluorescent sensor that exhibits unprecedented enantioselectivity for the recognition of diverse α-hydroxycarboxylic acids.

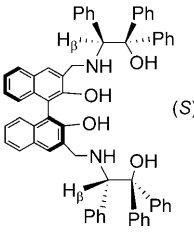


(*S*)-**1**

Initial structural modifications of (*S*)-**1** were performed by introducing various R substituents at the chiral amine centers to afford derivatives (*S*)-**2a**–**2e**. However, when these compounds interacted with α-hydroxycarboxylic acids, their fluorescent responses were indicative of poorer enantioselectivity; thus, the reduced steric bulk at the terminal hydroxy sites had reduced the enantioselectivity of the fluorescent responses. Therefore, the BINOL amino alcohol compound (*S*)-**3**, which has very bulky tertiary hydroxy groups, was synthesized and its fluorescent response studied. We found that the increased steric bulk in (*S*)-**3** led to high enantioselectivity in the fluorescent recognition of various α-hydroxycarboxylic acids.



(*S*)-**2a** R = Me
(*S*)-**2b** R = *i*-Pr
(*S*)-**2c** R = *i*-Bu
(*S*)-**2d** R = t-Bu
(*S*)-**2e** R = Ph



(*S*)-**3**

The UV/Vis spectrum of (*S*)-**3** in benzene showed absorptions at $\lambda_{max} = 281$, 292, and 334 nm. The fluorescence spectrum of (*S*)-**3** in benzene showed an emission signal at $\lambda =$ 374 nm (Figure 1). Although no change was observed for the UV/Vis absorption wavelengths of (*S*)-**3** when the solvent was changed to dichloromethane, the fluorescence spectrum displayed two emissions, at $\lambda = 372$ and 448 nm, that are very different from that in benzene. The ratio of the long-wavelength to short-wavelength emission in dichloromethane was found to increase as the concentration of (*S*)-**3** increases. The long-wavelength signal was assigned to the excimer emission and the short-wavelength signal to monomer emission. The excimer emission of (*S*)-**3** is probably due to an intermolecular association between the aromatic rings of this compound. As benzene solvates the aromatic rings of (*S*)-**3** better than dichloromethane, this should contribute to the much less intense excimer emission observed in benzene than in dichloromethane. The more polar dichloromethane should interact with the polar amine groups and hydroxy groups of (*S*)-**3** more strongly, which might encourage intermolecular association between the aromatic rings for an enhanced excimer emission. The X-ray structure of (*S*)-**3** crystallized from a polar solvent (ethanol) also reveals an intermolecular interaction between the aromatic rings of (*S*)-**3** (Supporting Information, Figure S1).[9]

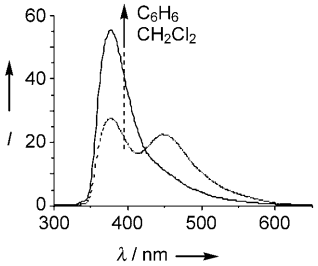


Figure 1. Fluorescence spectra of (*S*)-**3** in benzene, and in dichloromethane, at 5.0×10^{-4} mol L^{-1}. ($\lambda_{exc} = 334$ nm, slit = 5.0/5.0 nm).

The fluorescent responses of (*S*)-**3** towards a variety of α-hydroxycarboxylic acids (Scheme 1) are summarized in the Supporting Information (Figure S2). As an example, the interaction of (*S*)-**3** with phenyllactic acid (**7**) is shown (Figure 2). A benzene solution of (*S*)-**3** (2.0×10^{-4} mol L^{-1}) was treated with the individual enantiomers of **7** over the concentration range 1.0×10^{-3}–5.0×10^{-3} mol L^{-1}. 1,2-Dimethoxyethane (DME, 0.4% v/v) was added to the solution to improve the solubility of the acid in benzene. Whilst (*S*)-**7** quenches the monomer emission of the sensor and enhances the excimer emission, (*R*)-**7** greatly enhances the monomer emission of (*S*)-**3** (Figure 2a). The ratio of the fluorescence intensities for the monomer emission, that is I_R/I_S (or I_S/I_R), can be used to represent the enantioselectivity of the sensor toward the α-hydroxycarboxylic acids under investigation. I_R/I_S ratios of up to 11.2 are observed for the interaction of (*S*)-**3** with **7**. To our knowledge, this is the first reported fluorescent recognition of phenyllactic acid with such high enantioselectivity.

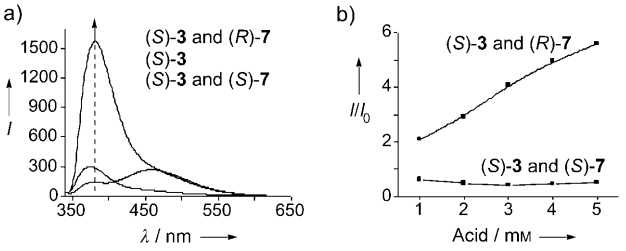
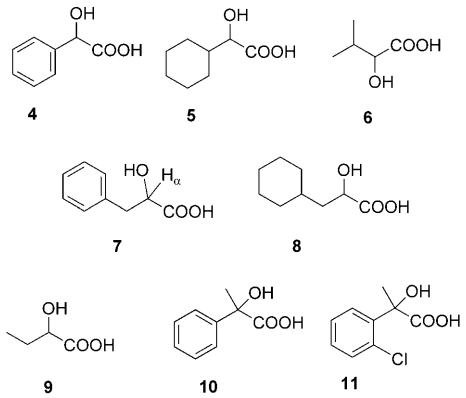


Figure 2. a) Fluorescence spectra of (*S*)-**3** (2.0×10^{-4} mol L^{-1} in benzene, 0.4% v/v DME) with (*R*)-**7** or (*S*)-**7** (5.0×10^{-3} mol L^{-1}). b) Fluorescence enhancement of (*S*)-**3** at various concentrations of (*R*)-**7** or (*S*)-**7** at $\lambda_{em.} = 382$ nm ($\lambda_{exc} = 334$ nm, slit = 5.0/5.0 nm).

The enantioselectivity of (*S*)-**3** towards **7** was compared with that towards mandelic acid (**4**). When (*S*)-**3** was treated with (*R*)-**4** under the same conditions, the monomer emission was greatly enhanced; when (*S*)-**3** was treated with the other enantiomer, (*S*)-**4**, the monomer emission was slightly quenched and there was a significant enhancement in the excimer emission. I_R/I_S ratios of up to 4.0 were observed for the monomer emission of (*S*)-**3**. Thus, the fluorescent sensor (*S*)-**3** is highly enantioselective toward both mandelic acid and phenyllactic acid, with the enantioselectivity significantly higher for **7** than for **4**. This is particularly noteworthy as **7** contains a flexible methylene unit between the benzene ring and the α position of the acid; this has previously led to much lower enantioselectivities for **7** than for **4** in fluorescent recognition.[7d]

The fluorescent responses of (*S*)-**3** in the presence of (*R*)- and (*S*)-hexahydromandelic acid (**5**), the hydrogenated derivative of **4**, was then studied. (*R*)-**5** was found to greatly enhance the monomer emission of (*S*)-**3**, with a much smaller change observed for excimer emission. The other enantiomer, (*S*)-hexahydromandelic acid, quenched the monomer emission of (*S*)-**3** whilst also enhancing excimer emission. For the monomer emission, the I_R/I_S ratio was found to be as high as 25.8 in the concentration range 1.0×10^{-3}–5.0×10^{-3} mol L^{-1}. The fluorescent responses of the sensor towards the enantiomers of a second β-branched α-hydroxycarboxylic acid, α-hydroxyisovaleric acid (**6**), gave I_R/I_S ratios of up to 11.2.



Scheme 1. Chiral α-hydroxycarboxylic acids.

When (*S*)-**3** interacted with the enantiomers of hexahydrophenyllactic acid (**8**), the hydrogenated derivative of **7**, it showed even higher enantioselective responses than with **7**. For the monomer emission of (*S*)-**3**, the observed I_R/I_S ratios were up to 22.8. Therefore, the more sterically demanding hydrogenated derivatives **8** and **5** exhibited significantly greater enantioselectivity than **7** and **4**, respectively.

(*S*)-**3** was then used to investigate the recognition of enantiomers of a linear unbranched aliphatic α-hydroxycarboxylic acid, α-hydroxybutyric acid (**9**). As before, (*R*)-**9** significantly enhances the monomer emission of (*S*)-**3**, and (*S*)-**9** quenches the monomer emission. I_R/I_S ratios of up to 13.9 were obtained. This is the first example of the highly enantioselective fluorescent recognition of a linear aliphatic α-hydroxycarboxylic acid.

The ability of the sensor (*S*)-**3** to recognize a tertiary α-hydroxycarboxylic acid, atrolactic acid (**10**), was also considered. It was found that (*S*)-**10** quenched the monomer emission of (*S*)-**3**, and that enantiomer (*R*)-**10** greatly enhanced it. At the monomer emission wavelength, I_R/I_S ratios of up to 13.0 were observed. The interaction of tertiary α-hydroxycarboxylic acid **11** with (*S*)-**3** was also studied. (*S*)-**11** quenched the monomer emission of (*S*)-**3** slightly whereas its enantiomer (*R*)-**11** enhanced it. At the monomer emission wavelength, I_R/I_S ratios of up to 2.4 were observed. This is the first reported example of a highly enantioselective fluorescent sensor for the recognition of α-*tert*-hydroxycarboxylic acids.

The enantioselective fluorescent recognition of chiral acids by (*S*)-**3** was confirmed using sensor (*R*)-**3**, which gave the expected mirror image responses for the enantiomers of all of the tested chiral acids.

The fluorescent responses of (*S*)-**3** in an enantiomeric mixture of **7** were also investigated. The fluorescent enhancement of the sensor at 382 nm had an almost linear relationship with the enantiomeric composition of the α-hydroxycarboxylic acid (Figure 3a, Curve B). Therefore, from the fluorescence measurement, the enantiomeric purity of the acid could be determined. Curve A shows the fluorescence enhancement of (*S*)-**3** in the presence of the enantiomerically pure (*R*)-**7** (Figure 3a). The difference between the two curves in Figure 3a is due to the fluorescence quenching by (*S*)-**7** at the monomer emission of (*S*)-**3**.

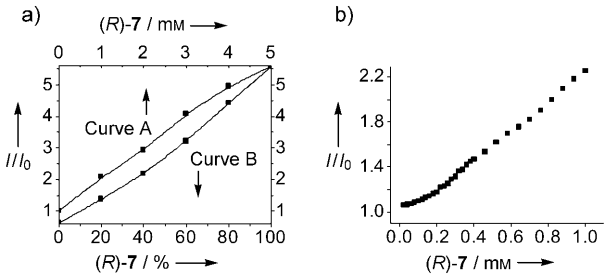


Figure 3. a) Fluorescence enhancement of (*S*)-**3** (2.0×10^{-4} mol L^{-1}, benzene/0.4% DME (%v/v)) in the presence of enantiomerically pure (*R*)-**7** (Curve A) and a mixture of (*R*)-**7** and (*S*)-**7** at 5.0×10^{-3} mol L^{-1} (Curve B) ($\lambda_{exc}=334$ nm, slit = 5.0/5.0 nm). b) Fluorescence enhancement of (*S*)-**3** (2.0×10^{-4} mol L^{-1}) at $\lambda_{em}=382$ nm when titrated with (*R*)-**7** (0–1.0 m mol L^{-1}). ($\lambda_{exc}=334$ nm, slit = 5.0/5.0 nm).

The interaction of (*R*)-**7** with (*S*)-**3** has also been investigated using ^{1}H NMR spectroscopy. A mixed solvent system of [D$_6$]benzene/[D$_6$]acetone (96:4) was used, and the total concentration of (*S*)-**3** and(*R*)-**7** was maintained at 6.0×10^{-3} mol L^{-1}. The H_α signal of (*R*)-**7** at $\delta=4.414$ ppm (dd) was shifted upfield; the most pronounced shift ($\Delta\delta_{max}=0.16$) was observed at an (*S*)-**3**/(*R*)-**7** ratio of 1:1 (Supporting Information, Figure S3). The chemical shift of the H_β signal of (*S*)-**3** with respect to the concentration of (*R*)-**7** was also examined. In the absence of (*R*)-**7**, the chemical shift of the H_β proton of (*S*)-**3** was 4.639 ppm. This signal underwent a small downfield shift when treated with (*R*)-**7** but no $\Delta\delta_{max}$ was observed (Supporting Information, Figure S4). The Job plot (Supporting Information, Figure S5) obtained from the ^{1}H NMR data of the H_β proton of (*S*)-**3** showed multiple binding modes between (*S*)-**3** and (*R*)-**7**. The largest change in the ^{1}H NMR signal of (*R*)-**7** was observed at a 1:1 ratio, though the chemical shift of (*S*)-**3** changes continuously with increasing (*R*)-**7**.

Figure 3b shows the fluorescence enhancement of (*S*)-**3** in the presence of (*R*)-**7** at concentration ratios of close to 1:1. A solution of (*S*)-**3** (2.0×10^{-4} mol L^{-1} in benzene/DME, 99.6:0.4, 3 mL) was titrated with (*R*)-**7** (6.0×10^{-2} mol L^{-1} in benzene/DME, 92.5:7.5) at 1 μL intervals. At an (*R*)-**7**/(*S*)-**3** ratio of less than one, that is at [(*R*)-**7**] < 0.2 mmol L^{-1}, the fluorescence enhancement rate was low. The fluorescence enhancement rate was much larger at concentrations of (*R*)-**7** of over 0.2 mmol L^{-1}.

On the basis of these NMR spectroscopy and fluorescence titration studies, we propose a two-stage interaction mechanism[7d] for the fluorescent recognition of (*R*)-**7** by (*S*)-**3**. In the first stage, (*S*)-**3** and (*R*)-**7** form a relatively stable 1:1 complex, held together by rigid hydrogen bonding that includes a strong interaction between the carboxylic acid proton of (*R*)-**7** and the (*S*)-**3** nitrogen atom. Although this 1:1 complex gives the most pronounced chemical shift change in the ^{1}H NMR spectrum of (*R*)-**7**, there is minimal fluorescence enhancement in (*S*)-**3**. This is because (*S*)-**3** contains an additional nitrogen atom that has not been protonated by (*R*)-**7** and is thus free to quench the fluorescence of the 1:1 complex between (*S*)-**3** and(*R*)-**7** by photoinduced electron transfer. During the second stage, further (probably weaker) interaction between the 1:1 complex and excess amount of (*R*)-**7** allows the protonation of the second nitrogen atom, which in turn enhances the fluorescence of the complex. This complex is an inherently stronger fluorophore than (*S*)-**3** alone, probably due to the increased structural rigidity.

A computational study of the 1:1 complex of (*S*)-**3** and (*R*)-**7** was performed using the Gaussian 03 program[10] with the density functional theory method B3LYP.[11] Geometries were optimized using the 6-31G basis set and energies were estimated using the 6-31G* basis set. In the complex, there are multiple functional group interactions between the α-hydroxycarboxylic acid (*R*)-**7** and the BINOL amino alcohol sensor (*S*)-**3**. The NH and BINOL hydroxy groups on the sensor may have strong base and acid interactions with the hydrogen atom on the COOH group and the oxygen of the C=O group in (*R*)-**7**, respectively. Therefore, as the three proposed modes show (Figure 4a), the α-hydroxy group of

(*R*)-**7** may form hydrogen bonds with the tertiary hydroxyl group of the sensor on the opposite side (A), on the same side (B), or on both sides (C) according to the orientation of the acid group in (*R*)-**7** combined with the NH group. The structure of mode C is shown in Figure 4b. This mode is calculated to be 4.3 kcal mol^{-1} and 1.7 kcal mol^{-1} more stable than modes A and B, respectively.

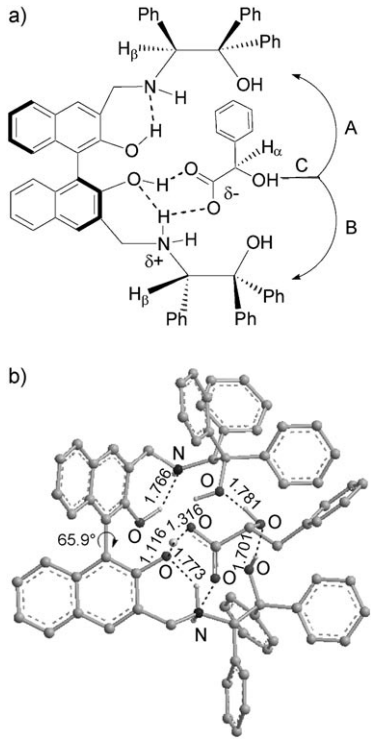


Figure 4. a) The modes, A–C of the proposed 1:1 complexation of (*S*)-**3** + (*R*)-**7.** b) Calculated structures of mode C. For clarity, most hydrogen atoms are omitted.

In summary, we have found that the easily accessible BINOL amino alcohol molecule (*S*)-**3** is a highly enantioselective fluorescent sensor for structurally diverse α-hydroxycarboxylic acids. This sensor exhibits an unprecedented enantioselectivity for phenyllactic acid, in addition to mandelic acid and hexahydromandelic acid. It is also the first highly enantioselective fluorescent sensor for the recognition of linear aliphatic α-hydroxycarboxylic acids and α-tertiary-hydroxycarboxylic acids. When (*S*)-**3** was treated with a chiral acid, one enantiomer of the acid greatly enhances its monomer emission whilst the opposite enantiomer quenches it. This effect leads to high enantioselectivities in the recognition of a variety of α-hydroxycarboxylic acids. Such sensors are potentially useful for high throughput chiral assays and chiral catalyst screening. Further work in this area is underway.

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[1] For reviews, see: a) M. T. Reetz, *Angew. Chem.* **2002**, *114*, 1391 – 1394; *Angew. Chem. Int. Ed.* **2002**, *41*, 1335 – 1338; b) M. Tsukamoto, H. B. Kagan, *Adv. Synth. Catal.* **2002**, *344*, 453 – 463; c) M. G. Finn, *Chirality* **2002**, *14*, 534 – 540; d) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885 – 1889.

[2] For selected examples, see: a) J. Guo, J. Wu, G. Siuzdak, M. G. Finn, *Angew. Chem.* **1999**, *111*, 1868 – 1871; *Angew. Chem. Int. Ed.* **1999**, *38*, 1755 – 1758; b) M. T. Reetz, M. H. Becker, H. W. Klein, D. Stöckigt, *Angew. Chem.* **1999**, *111*, 1872 – 1875; *Angew. Chem. Int. Ed.* **1999**, *38*, 1758 – 1761; c) M. T. Reetz, M. H. Becker, K. M. Kühling, A. Holzwarth, *Angew. Chem.* **1998**, *110*, 2792 – 2795; *Angew. Chem. Int. Ed.* **1998**, *37*, 2647 – 2650; d) M. T. Reetz, K. M. Kühling, A. Deege, H. Hinrichs, D. Belder, *Angew. Chem.* **2000**, *112*, 4049 – 4052; *Angew. Chem. Int. Ed.* **2000**, *39*, 3891 – 3893; e) K. Ding, A. Ishii, K. Mikami, *Angew. Chem.* **1999**, *111*, 519 – 523; *Angew. Chem. Int. Ed.* **1999**, *38*, 497 – 501; f) P. Abato, C. T. Seto, *J. Am. Chem. Soc.* **2001**, *123*, 9206 – 9207.

[3] a) For a Review on enantioselective fluorescent sensing, see: L. Pu, *Chem. Rev.* **2004**, *104*, 1687 – 1716. Selected Reviews on using fluorescence in sensing: b) T. D. James, M. D. Phillips, S. Shinkai, *Boronic Acids in Saccharide Recognition*, RSC, UK, **2006**; c) C. McDonagh, C. S. Burke, B. D. MacCraith, *Chem. Rev.* **2008**, *108*, 400 – 422; d) S. M. Borisov, O. S. Wolfbeis, *Chem. Rev.* **2008**, *108*, 423 – 461; e) K. S. Johnson, J. A. Needoba, S. C. Riser, W. J. Showers, *Chem. Rev.* **2007**, *107*, 623 – 640; f) R. Jelinek, S. Kolusheva, *Chem. Rev.* **2004**, *104*, 5987 – 6015; g) E. M. Nolan, S. J. Lippard, *Acc. Chem. Res.* **2009**, *42*, 193 – 203; h) R. B. Thompson, *Fluorescence Sensors and Biosensors*, CRC, U.S., **2005**; i) *Fluorescent Chemosensors for Ion and Molecular Recognition* (Ed.: A. W. Czarnik), American Chemical Society, Washington, DC, **1993** (ACS Symposium Series 538); j) A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.* **1997**, *97*, 1515 – 1566; k) L. Fabbrizzi, A. Poggi, *Chem. Soc. Rev.* **1995**, *24*, 197 – 202; l) *Fluorescent and Luminescent Probes*, 2nd ed. (Ed.: W. T. Mason), Academic, San Diego, **1999**; m) L. Basabe-Desmonts, D. N. Reinhoudt, M. Crego-Calama, *Chem. Soc. Rev.* **2007**, *36*, 993 – 1017.

[4] For examples using fluorescence in chiral analysis, see: a) T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Angew. Chem.* **1996**, *108*, 2038 – 2050; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1910 – 1922; b) T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Nature* **1995**, *374*, 345 – 347; c) A. P. de Silva, *Nature* **1995**, *374*, 310; d) M. Takeuchi, S. Yoda, T. Imada, S. Shinkai, *Tetrahedron* **1997**, *53*, 8335 – 8348; e) J. Z. Zhao, T. M. Fyles, T. D. James, *Angew. Chem.* **2004**, *116*, 3543 – 3546; *Angew. Chem. Int. Ed.* **2004**, *43*, 3461 – 3464; f) F. Han, L. N. Chi, X. F. Liang, S. M. Ji, S. S. Liu, F. K. Zhou, Y. B. Wu, K. L. Han, J. Z. Zhao, T. D. James, *J. Org. Chem.* **2009**, *74*, 1333 – 1336; g) V. Pugh, Q. S. Hu, L. Pu, *Angew. Chem.* **2000**, *112*, 3784 – 3787; *Angew. Chem. Int. Ed.* **2000**, *39*, 3638 – 3641; h) M. T. Reetz, S. Sostmann, *Tetrahedron* **2001**, *57*, 2515 – 2520; i) G. A. Korbel, G. Lalic, M. D. Shair, *J. Am. Chem. Soc.* **2001**, *123*, 361 – 362; j) E. R. Jarvo, C. A. Evans, G. T. Copeland, S. J. Miller, *J. Org. Chem.* **2001**, *66*, 5522 – 5527; k) W. L. Wong, K. H. Huang, P. F. Teng, C. S. Lee, H. L. Kwong, *Chem. Commun.* **2004**, 384 – 385; l) S. Pagliari, R. Corradini, G. Galaverna, S. Sforza, A. Dossena, M. Montalti, L. Prodi, N. Zaccheroni, R. Marchelli, *Chem. Eur. J.* **2004**, *10*, 2749 – 2758; m) G. Klein, J. L. Reymond, *Helv. Chim. Acta* **1999**, *82*, 400 – 407.

[5] a) L. Zhu, E. V. Anslyn, *J. Am. Chem. Soc.* **2004**, *126*, 3676 – 3677; b) L. Zhu, Z. Zhong, E. V. Anslyn, *J. Am. Chem. Soc.* **2005**, *127*, 4260 – 4269.

[6] a) F. Taran, C. Gauchet, B. Mohar, S. Meunier, A. Valleix, P. Y. Renard, C. Créminon, J. Grassi, A. Wagner, C. Mioskowski, *Angew. Chem.* **2002**, *114*, 132 – 135; *Angew. Chem. Int. Ed.* **2002**, *41*, 124 – 127; b) D. Yang, X. Li, Y. F. Fan, D. W. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 7996 – 7997; c) S. Shirakawa, A. Moriyama, S. Shimizu, *Org. Lett.* **2007**, *9*, 3117 – 3119.

[7] a) J. Lin, Q. S. Hu, M. H. Xu, L. Pu, *J. Am. Chem. Soc.* **2002**, *124*, 2088 – 2089; b) M. H. Xu, J. Lin, Q. S. Hu, L. Pu, *J. Am. Chem. Soc.* **2002**, *124*, 14239 – 14246; c) Z.-B. Li, J. Lin, L. Pu, *Angew. Chem.* **2005**, *117*, 1718 – 1721; *Angew. Chem. Int. Ed.* **2005**, *44*, 1690 – 1693; d) Z. B. Li, J. Lin, M. Sabat, M. Hyacinth, L. Pu, *J. Org. Chem.* **2007**, *72*, 4905 – 4916; e) H. L. Liu, X. L. Hou, L. Pu, *Angew. Chem.* **2009**, *121*, 388 – 391; *Angew. Chem. Int. Ed.* **2009**, *48*, 382 – 385; f) X. F. Mei, C. Wolf, *J. Am. Chem. Soc.* **2004**, *126*, 14736 – 14737; g) K. Dhara, K. Sarkar, P. Roy, M. Nandi, A. Bhaumik, P. Banerjee, *Tetrahedron* **2008**, *64*, 3153 – 3159.

[8] a) L. Chi, J. Z. Zhao, T. D. James, *J. Org. Chem.* **2008**, *73*, 4684 – 4687; b) A. A. Williams, S. O. Fakayode, M. Lowry, I. M. Warner, *Chirality* **2009**, *21*, 305 – 315; c) A. A. Williams, S. O. Fakayode, O. Alptürk, C. M. Jones, M. Lowry, R. M. Strongin, I. M. Warner, *J. Fluoresc.* **2008**, *18*, 285 – 296; d) J. Z. Zhao, M. G. Davidson, M. F. Mahon, G. Kociok-Köhn, T. D. James, *J. Am. Chem. Soc.* **2004**, *126*, 16179 – 16186.

[9] CCDC 755118 ((*S*)-**3**) contains 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.

[10] The calculations were performed using a Gaussian 03 program: Gaussian 03, revision D.01, M. J. Frisch, et al., Gaussian, Inc., Wallingford, CT, **2004**.

[11] a) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372; c) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; d) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.

