Chirality Inversion

International Edition: DOI: 10.1002/anie.201509479
German Edition: DOI: 10.1002/ange.201509479

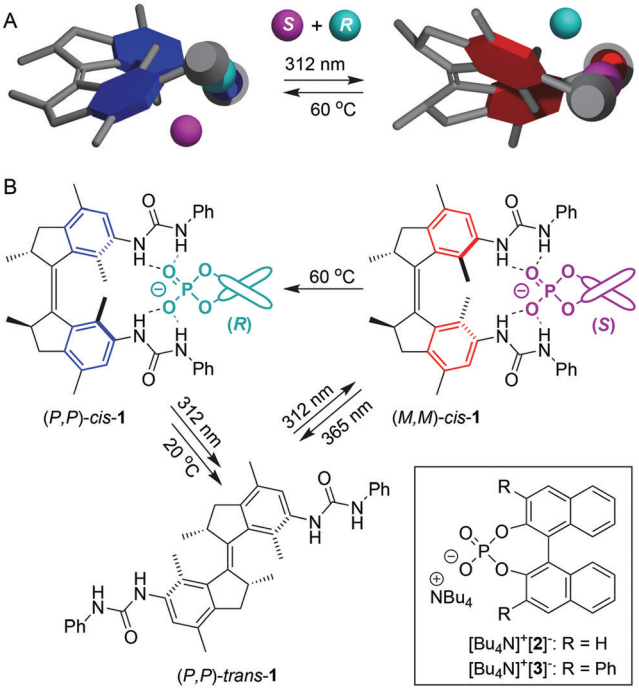
Dynamic Inversion of Stereoselective Phosphate Binding to a Bisurea Receptor Controlled by Light and Heat

Matea Vlatković, Ben L. Feringa, and Sander J. Wezenberg**

Abstract: *A chiral bisurea anion receptor, derived from a first-generation molecular motor, can undergo photochemical and thermal isomerization operating as a reconfigurable system. The two possible cis configurations in the isomerization cycle are opposite in helicity, as is shown by CD spectroscopy. ^{1}H NMR titrations demonstrate that the P and M helical cis isomers hold opposite enantioselectivity in the binding of binol phosphate, while anion complexation by the intermediate trans isomer is not selective. The difference in the binding affinity of the enantiomers was rationalized by DFT calculations, revealing very distinct binding modes. Thus, the enantiopreferred substrate binding in this receptor can be inverted in a dynamic fashion using light and heat.*

Since the earliest development of molecules with structure-specific interactions by Cram, Lehn, and Pedersen,[1] chemists have been highly active in the area of chiral recognition and especially enantioselective discrimination.[2] The obvious reason is that the vast majority of biomolecules is chiral and the ability of proteins to distinguish between enantiomers is of fundamental importance to various biological processes, for example, signal transduction, drug binding, and catalysis.[3] In principle, the enantiopreference of any biological or chemical receptor is fixed by the chiral building blocks that it is made from. Yet, we were intrigued by the possibility to develop a chirality-switchable receptor that could selectively bind a given enantiomer in one state, whereas in the other state it prefers binding the opposite enantiomer (Scheme 1 A). Such a receptor could be used to dynamically control the ratio between enantiomers or selectively transport an enantiomer of choice. Knowing that opposite enantiomers of chiral substrates can produce entirely different effects,[4] this may be applied eventually also to exert unique control over chirality-responsive biological and chemical processes.

Dynamic control of chirality has been successfully demonstrated in synthetic systems over the past years, ranging from helical polymers[5] and cholesteric liquid crystals[6] to enantioselective catalysts.[7] For example, Yashima, Maeda, and co-workers showed inversion of the elution order of enantiomers in chromatographic separation by making use of a dynamic helical polyacetylene as the stationary phase.[8]



Scheme 1. A) Schematic representation of a chirality-switchable receptor. B) Isomerization and coordination behavior of bisurea receptor **1**. The (*P,P*)-*trans*:(*M,M*)-*cis* ratio at the photostationary state (PSS_{312}) is 20:80 and the thermal half-life ($t_{1/2}$) of (*M,M*)-*cis*-**1** is 147 h at 20 °C.[12] The enantioselectivity for chiral binol phosphate is inverted upon light- and heat-induced switching between the *cis* isomers.

Furthermore, Aida and co-workers observed an interesting inversion of the helical bisporphyrin orientation in a photoresponsive host, which has been used to manipulate the conformation of a guest molecule.[9] A helix inversion process is also inherent to the thermally activated step in unidirectional rotary molecular motors developed in our group.[10] Equipment of molecular motors with catalytic functions has made it possible to control the stereoselectivity in a chemical reaction.[7b,11]

Recently, we have described bisurea receptor **1** (Scheme 1 B),[12] which is derived from a first-generation molecular motor. This receptor can be photochemically and thermally switched between three isomers that all have distinct anion-binding affinities (that is, for phosphate and acetate anions).[13] As a result of the important and diverse roles played by anions in biology, the development of synthetic receptors for anionic substrates is receiving enormous interest.[14] In this context, enantioselective binding and extraction of chiral anions is an important challenge.[15,16]

In this study, we have prepared enantiopure **1** of which the *P* and *M* helical *cis* isomers can be easily interconverted using

[*] M. Vlatković, Prof. Dr. B. L. Feringa, Dr. S. J. Wezenberg
Stratingh Institute for Chemistry
University of Groningen
Nijenborgh 4, 9747 AG, Groningen (The Netherlands)
E-mail: b.l.feringa@rug.nl
s.j.wezenberg@rug.nl

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509479.

light and heat (Scheme 1B). Interestingly, we discovered that the isomers (*P*,*P*)-*cis*-**1** and (*M*,*M*)-*cis*-**1** hold opposite enantioselectivity in the binding of chiral binol phosphate. Thus, the enantiopreference exhibited by **1** can be inverted in a dynamic fashion and, to the best of our knowledge, this is the first time that such responsive behavior is demonstrated using a chiral receptor.

Bisurea receptor (*P*,*P*)-*cis*-**1** was synthesized analogously to the previously reported (±)-*cis*-**1**,[12] although in the present study we started from the enantiopure dibromide precursor.[17] The photochemical and thermal switching between stable (*P*,*P*)-*cis*-**1** and unstable[18] (*M*,*M*)-*cis*-**1** was monitored with UV/Vis absorption and circular dichroism (CD) spectroscopies (Figure 1A). Irradiation of a solution of stable (*P*,*P*)-*cis*-**1** with light of wavelength $\lambda = 312$ nm resulted in a bathochromic shift of the bands in the UV/Vis absorption spectrum and an inversion of the CD signal, which is consistent with conversion to (*M*,*M*)-*cis*-**1**.[10,19] Upon subsequent heating of the sample, the spectra returned to their original shapes indicating the regeneration of the stable *cis* form.[20] Furthermore, as is illustrated in Figure 1B this light- and heat-controlled helix inversion process could be repeated over multiple cycles without significant signs of fatigue.

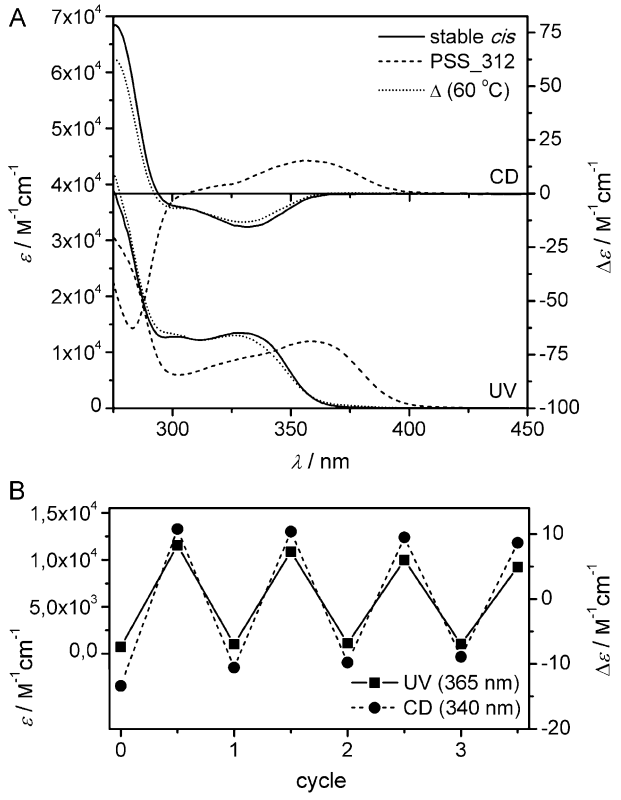


Figure 1. A) CD (upper) and UV/Vis absorption (lower) spectra of (*P*,*P*)-*cis*-**1** (5×10^{-4} M in DMSO) before (trace denoted stable *cis*) and after (denoted PSS_312) irradiation with light of wavelength $\lambda = 312$ nm at 20°C and after heating at 60°C for 6 h (trace labelled Δ(60°C)). B) Change in the CD ($\lambda = 340$ nm) and UV/Vis absorption ($\lambda = 365$ nm) intensities upon alternating irradiation and heating. ε = molar extinction coefficient ($M^{-1}\,cm^{-1}$).

The binol-derived phosphate salts $[Bu_4N]^+[\mathbf{2}]^-$ and $[Bu_4N]^+[\mathbf{3}]^-$ were obtained by treatment of the respective phosphoric acids with tetrabutylammonium hydroxide in methanol (see the Supporting Information for details). The stability constants (K_a) for complexation of either enantiomer of these phosphates by the interchangeable isomers of bisurea receptor **1** (see Scheme 1) were determined by ^{1}H NMR titrations in [D$_6$]DMSO/0.5% H_2O. Stepwise addition of $[Bu_4N]^+[(S)\text{-}\mathbf{2}]^-$ and $[Bu_4N]^+[(R)\text{-}\mathbf{2}]^-$ to (*P*,*P*)-*cis*-**1** led to downfield shifts of the signals attributable to urea (Figures S7–8 in the Supporting Information), which is indicative of anion binding. Fitting of the titration data to a 1:1 binding model with the use of HypNMR software[21] revealed a strong preference for binding of the *R* enantiomer over the *S* enantiomer ($K_R/K_S = 4.2$; Table 1 and Figure S17 in the Supporting Information).[22] On the other hand, titrations to (*P*,*P*)-*trans*-**1**[23] revealed poor binding ($K_a < 20\,M^{-1}$) and no enantioselectivity (Figures S9–10 and S18).

Table 1: Binding constants of chiral binol phosphates[a] to bisurea **1** (K_R, K_S; M^{-1}) and differences in free energies of complexation ($\Delta\Delta G^{298}$; kJ mol^{-1}).[b]

	(*S*)-**2**	(*R*)-**2**	$\Delta\Delta G^{298}$ (**2**)	(*S*)-**3**	(*R*)-**3**	$\Delta\Delta G^{298}$ (**3**)
(*P*,*P*)-*cis*-**1**	100	415	3.53	17[c]	94	4.24
(*M*,*M*)-*cis*-**1**	55	17[c]	2.91	–[d]	–[d]	

[a] Phosphates were added stepwise as the tetrabutylammonium salt; [**1**] = 5 mM in [D$_6$]DMSO/0.5% H_2O, [phosphate] = 0.1 M in a solution of **1**. [b] Calculated using $\Delta\Delta G° = |RT\ln(K_S/K_R)|$. [c] Although fitted to a 1:1 model, simultaneous 2:1 complexation cannot be excluded. [d] ^{1}H NMR spectral changes are too small for calculation of a stability constant.

To determine a stability constant for complexation of **2** by (*M*,*M*)-*cis*-**1**, competitive titrations to the photostationary-state (at $\lambda = 312$ nm) mixture (PSS_{312}; *cis*:*trans* = 80:20)[12] were carried out under the same conditions. In this case, the titration data were evaluated considering the simultaneous formation of both (*M*,*M*)-*cis*-**1** and (*P*,*P*)-*trans*-**1** phosphate complexes using the known constants for the latter (Figures S11–12 and S19). It was found that now the *S* enantiomer of **2** binds the strongest ($K_S/K_R = 3.2$; Table 1). However, in addition to stereoselective inversion, a decrease in binding strength was noted when going from (*P*,*P*)-*cis*-**1** to (*M*,*M*)-*cis*-**1**. This was previously also observed for the binding of dihydrogen phosphate to (±)-**1** and has been explained by a difference in the central C=C dihedral angle.[12] Nevertheless, these studies clearly demonstrate that the enantioselective binding of chiral phosphate exhibited by bisurea receptor **1** is inverted upon photochemical and thermal isomerization.

Increase of the steric bulk through the introduction of *ortho*-phenyl substituents to the binol scaffold (compound **3**, see Scheme 1) was expected to improve the selectivity. Titrations of $[Bu_4N]^+[(S)\text{-}\mathbf{3}]^-$ and $[Bu_4N]^+[(R)\text{-}\mathbf{3}]^-$ to (*P*,*P*)-*cis*-**1** revealed indeed an increased *R*:*S* ratio ($K_R/K_S = 5.5$; Table 1, Figure S20). However, this *ortho* substitution goes at the cost of the binding strength and as a result, a stability constant for complexation by (*M*,*M*)-*cis*-**1** could not be calculated.

To gain a better understanding of the difference in binding mode of (*S*)-**2** and (*R*)-**2** to either (*P*,*P*)-*cis*-**1** or (*M*,*M*)-*cis*-**1**, geometry optimizations were performed on the B3LYP/6–31G++ (d,p) level of theory using an IEFPCM, DMSO solvation model (see the Supporting Information for details). The energy minimized diastereomeric complexes of [(*P*,*P*)-*cis*-**1**⊃(*S*)-**2**]$^-$ (Figure 2 A, C) and [(*P*,*P*)-*cis*-**1**⊃(*R*)-**2**]$^-$ (Figure 2 B, D) show very different orientations of the chiral phosphate anion. For example, where the naphthyl rings in (*S*)-**2** are closely parallel with the plane in which the phenylurea substituents are located, those in (*R*)-**2** are virtually orthogonal. The latter binding mode results in less steric crowding as is evident from the larger distance between naphthyl and phenylurea groups. This is consistent with the fewer downfield shifted ^{1}H NMR resonance signals attributable to urea for [Bu_4N]$^+$[(*P*,*P*)-*cis*-**1**⊃(*S*)-**2**]$^-$ as compared to those for [Bu_4N]$^+$[(*P*,*P*)-*cis*-**1**⊃(*R*)-**2**]$^-$ (Figures S7–8), in which the urea-NH protons experience less shielding. Furthermore, the orthogonal binding mode appears to favor edge-to-face CH/π interactions between the naphthyl rings and the aromatic protons of the phenylurea substituents ($CH_{ortho}\cdots\pi = 3.4$ Å, $CH_{meta}\cdots\pi = 3.7$ Å), which is reflected in pronounced upfield ^{1}H NMR shifts. Both these features explain the higher stability for [(*P*,*P*)-*cis*-**1**⊃(*R*)-**2**]$^-$, which based on these calculations was found to be 3.43 kJ mol^{-1} lower in energy than [(*P*,*P*)-*cis*-**1**⊃(*S*)-**2**]$^-$. This is in good agreement with the experimental result (Table 1). Analysis of the structures calculated for (*M*,*M*)-*cis*-**1** showed comparable results and here, in line with experiment, the lowest energy complex has (*S*)-**2** bound (SCF zero-point energy difference $\Delta E_{298} = 3.34$ kJ mol^{-1}; see Table S1–4 in the Supporting Information).

In conclusion, we have shown that the (*P*,*P*)-*cis* and (*M*,*M*)-*cis* isomers of bisurea receptor **1**, which can be interconverted using light and heat, exhibit opposite enantiopreferences for the binding of binol phosphate. To our knowledge, this is the first example of a receptor in which the enantioselectivity toward a chiral substrate can be inverted in a dynamic fashion. Our future research is aimed at modification of the recognition site for achieving strong and selective binding of biologically relevant phosphates and acetates, for instance, DNA and amino acids.

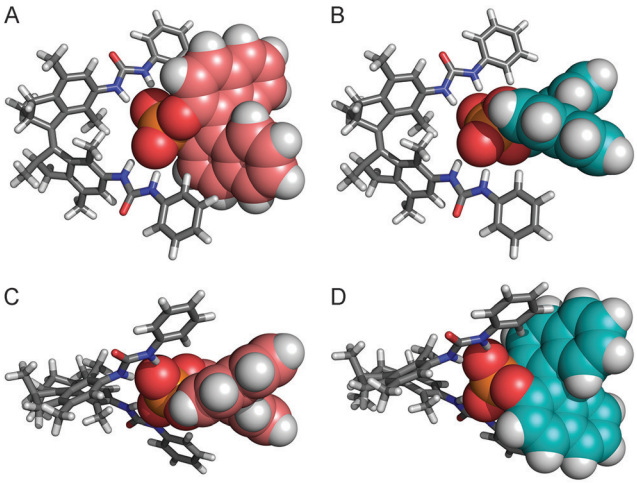


Figure 2. B3LYP/6–31G++(d,p) optimized geometries of A, C) [(*P*,*P*)-*cis*-**1**⊃(*S*)-**2**]$^-$ and B, D) [(*P*,*P*)-*cis*-**1**⊃(*R*)-**2**]$^-$ showing top (A, B) and side (C, D) views.

Acknowledgements

This work was financially supported by The Netherlands Organization for Scientific Research (NWO-CW, Veni grant to S.J.W.), the Ministry of Education, Culture and Science (Gravitation program 024.001.035), and the European Research Council (Advanced Investigator Grant, no. 227897 to B.L.F).

Keywords: anions · chiral recognition · chirality inversion · molecular switches · photochromism

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 1001–1004
Angew. Chem. **2016**, *128*, 1013–1016

[1] a) J.-M. Lehn, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89–112; *Angew. Chem.* **1988**, *100*, 91–116; b) D. J. Cram, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009–1020; *Angew. Chem.* **1988**, *100*, 1041–1052; c) C. J. Pedersen, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021–1027; *Angew. Chem.* **1988**, *100*, 1053–1059.
[2] a) D. J. Cram, J. M. Cram, *Acc. Chem. Res.* **1978**, *11*, 8–14; b) J. F. Stoddart in *Topics in Stereochemistry*, *Vol. 17* (Eds.: E. L. Eliel, S. H. Wilen), Wiley, New York, **1987**, pp. 207–288; c) X. X. Zhang, J. S. Bradshaw, R. M. Izatt, *Chem. Rev.* **1997**, *97*, 3313–3361.
[3] J. M. Berg, J. L. Tymoczko, L. Stryer in *Biochemistry, 5th Ed.*, W. H. Freeman, New York, **2002**.
[4] a) M. R. Islam, J. G. Mahdi, I. D. Bowen, *Drug Saf.* **1997**, *17*, 149–165; b) *D-Amino Acids in Chemistry, Life Sciences, and Biotechnology* (Eds.: H. Brückner, N. Fujii), Wiley-VCH, Weinheim, **2011**.
[5] a) E. Yashima, K. Maeda, Y. Furusho, *Acc. Chem. Res.* **2008**, *41*, 1166–1180; b) E. Yashima, K. Maeda, *Macromolecules* **2008**, *41*, 3–12; c) D. Pijper, B. L. Feringa, *Soft Matter* **2008**, *4*, 1349–1372; d) H. Miyake, H. Tsukube, *Chem. Soc. Rev.* **2012**, *41*, 6977–6991.
[6] a) R. Eelkema, M. M. Pollard, J. Vicario, N. Katsonis, B. Serrano Ramon, C. W. M. Bastiaansen, D. J. Broer, B. L. Feringa, *Nature* **2006**, *440*, 163; b) N. Katsonis, E. Lacaze, A. Ferrarini, *J. Mater. Chem.* **2012**, *22*, 7088–7097; c) Y. Wang, Q. Li, *Adv. Mater.* **2012**, *24*, 1926–1945.
[7] a) T. Yamamoto, T. Yamada, Y. Nagata, M. Suginome, *J. Am. Chem. Soc.* **2010**, *132*, 7899–7901; b) J. Wang, B. L. Feringa, *Science* **2011**, *331*, 1429–1432; c) S. Mortezaei, N. R. Catarineu, J. W. Canary, *J. Am. Chem. Soc.* **2012**, *134*, 8054–8057; d) M. Suginome, T. Yamamoto, Y. Nagata, T. Yamada, Y. Akai, *Pure Appl. Chem.* **2012**, *84*, 1759–1769.
[8] K. Shimomura, T. Ikai, S. Kanoh, E. Yashima, K. Maeda, *Nat. Chem.* **2014**, *6*, 429–434.
[9] T. Muraoka, K. Kinbara, T. Aida, *Nature* **2006**, *440*, 512–515.
[10] a) N. Koumura, R. W. J. Zijlstra, R. A. van Delden, N. Harada, B. L. Feringa, *Nature* **1999**, *401*, 152–155; b) B. L. Feringa, *J. Org. Chem.* **2007**, *72*, 6635–6652.
[11] a) M. Vlatković, L. Bernardi, E. Otten, B. L. Feringa, *Chem. Commun.* **2014**, *50*, 7773–7775; b) D. Zhao, T. M. Neubauer, B. L. Feringa, *Nat. Commun.* **2015**, *6*, 1–7.

[12] S. J. Wezenberg, M.. Vlatković, J. C. M. Kistemaker, B. L. Feringa, *J. Am. Chem. Soc.* **2014**, *136*, 16784 – 16787.
[13] For related photoresponsive anion receptors see: a) T. Shimasaki, S.-i. Kato, K. Ideta, K. Goto, T. J. Shinmyozu, *J. Org. Chem.* **2007**, *72*, 1073 – 1087; b) Y. Hua, A. H. Flood, *J. Am. Chem. Soc.* **2010**, *132*, 12838 – 12840; c) Y. Wang, F. Bie, H. Jiang, *Org. Lett.* **2010**, *12*, 3630 – 3633; d) Z. Li, C. Zhang, Y. Ren, J. Yin, S. H. Liu, *Org. Lett.* **2011**, *13*, 6022 – 6025; e) S. Lee, Y. Hua, A. H. Flood, *J. Org. Chem.* **2014**, *79*, 8383 – 8396.
[14] a) J. L. Sessler, P. A. Gale, W.-S. Cho in *Anion Receptor Chemistry* (Ed.: J. F. Stoddart), RSC, London, **2006**; b) F. P. Schmidtchen, *Coord. Chem. Rev.* **2006**, *250*, 2918 – 2928; c) *Anion Coordination Chemistry* (Eds.: K. Bowman-James, A. Bianchi, E. García-España,), Wiley-VCH, Weinheim, **2012**; d) P. A. Gale, N. Busschaert, C. J. E. Haynes, L. E. Karagiannidis, I. L. Kirby, *Chem. Soc. Rev.* **2014**, *43*, 205 – 241.
[15] I. Stibor, P. ZlatuŠková, *Top. Curr. Chem.* **2005**, *255*, 31 – 63.
[16] For selected examples, see: a) A. Echavarren, A. Galán, J. M. Lehn, J. de Mendoza, *J. Am. Chem. Soc.* **1989**, *111*, 4994 – 4995; b) J. L. Sessler, A. Andrievsky, V. Král, V. Lynch, *J. Am. Chem. Soc.* **1997**, *119*, 9385 – 9392; c) I. Alfonso, B. Dietrich, F. Rebolledo, V. Gotor, J.-M. Lehn, *Helv. Chim. Acta* **2001**, *84*, 280 – 295; d) L. H. Uppadine, F. R. Keene, P. D. Beer, *J. Chem. Soc. Dalton Trans.* **2001**, 2188 – 2198; e) H. Miyaji, S.-J. Hong, S.-D. Jeong, D.-W. Yoon, H.-K. Na, J. Hong, S. Ham, J. L. Sessler, C.-H. Lee, *Angew. Chem. Int. Ed.* **2007**, *46*, 2508 – 2511; *Angew. Chem.* **2007**, *119*, 2560 – 2563; f) F. Wang, R. Nandhakumar, Y. Hu, D. Kim, K. M. Kim, J. Yoon, *J. Org. Chem.* **2013**, *78*, 11571 – 11576; g) J. M. Granda, J. Jurczak, *Org. Lett.* **2013**, *15*, 4730 – 4733.
[17] T. M. Neubauer, T. van Leeuwen, D. Zhao, A. S. Lubbe, J. C. M. Kistemaker, B. L. Feringa, *Org. Lett.* **2014**, *16*, 4220 – 4223.
[18] The term "unstable" refers here to a higher energy, metastable state and is not related to the chemical stability.
[19] Irradiation of stable (*P*,*P*)-*cis*-**1** first gives unstable (*M*,*M*)-*trans*-**1**, but this isomer has a half-life in the order of seconds at 20 °C (see Ref. [10]). Thus, unstable (*M*,*M*)-*cis*-**1** is obtained directly in a three-step process.
[20] It should be noted that also around 20 % (based on the PSS_{312} ratio) of the stable (*P*,*P*)-*trans*-**1** isomer is present in solution since it forms during the photochemical step (see Scheme 1).
[21] C. Frassineti, S. Ghelli, P. Gans, A. Sabatini, M. S. Moruzzi, A. Vacca, *Anal. Biochem.* **1995**, *231*, 374 – 382.
[22] Comparable selectivity was found for the oxo anion (that is, for lactate $K_R/K_S = 4.4$ and for 2-phenylbutyrate $K_S/K_R = 4.6$) binding to nonresponsive (*S*)-binaphthalene-based bisurea receptors: a) I. Stibor, R. Holakovský, A. R. Mustafina, P. Lhoták, *Collect. Czech. Chem. Commun.* **2004**, *69*, 365 – 383; b) K. M. K. Swamy, N. J. Singh, J. Yoo, S. K. Kwon, S.-Y. Chung, C.-H. Lee, J. Yoon, *J. Inclusion Phenom. Macrocyclic Chem.* **2010**, *66*, 107 – 111.
[23] (*P*,*P*)-*trans*-**1** was generated from (*P*,*P*)-*cis*-**1** by sequential irradiation with light of wavelengths $\lambda = 312$ and 365 nm.

Received: October 9, 2015
Published online: December 7, 2015

