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Planar-Chiral Thioureas as Hydrogen-Bond Catalysts

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The synthesis of the first enantiopure planar-chiral thiourea catalysts is herewith described. New catalysts **1**–**3** were applied in asymmetric transformations, such as the Friedel–Crafts alkylation of indole, as well as in the transfer hydrogenation of nitroolefins. Bifunctional catalysts **2** and **3** exhibit enhanced activity in the investigated reactions, demonstrating their potential for organic synthesis.

Introduction

Planar-chiral motifs are typically potent structural elements of chiral ligands for transition-metal[1] or nucleophilic catalysis.[2] These structures are usually derived from metallocenes, including ferrocene,[3] or from the [2.2]paracyclophane (Pc) framework.[4] In transition-metal catalysis, [2.2]paracyclophane has been predominantly recognized as a scaffold for phosphane ligands[5] or for N-heterocyclic carbenes.[6] 4,12-Bis(hydroxy)[2.2]paracyclophane (PHANOL) has been employed as a Brønsted acid organocatalyst.[7] The activation of substrates by small organic molecules through covalent- or Brønsted acid interactions has been proved as a complementary approach to transition-metal catalysis.[8] Hydrogen-bond catalysis[9] has attracted considerable attention. Moreover, highly efficient thiourea-based bifunctional organocatalysts have been explored in terms of their potential in asymmetric organic synthesis. The most commonly applied catalyst structures are derived from *trans*-cyclohexyldiamine, 2,2′-binaphthyl, amino acids, or the cinchona alkaloids.[10] Much to our surprise, there are no reports to date of planar-chiral (thio)urea structures being used as hydrogen-bond catalysts.

The [2.2]paracyclophane scaffold exhibits a rigid conformation, enabling the arrangement of functional groups within a defined distance (Figure 1, **I** and **II**). Such a rigid alignment should be beneficial for the spacial alignment of the catalytically active sites. Bifunctional catalysts[11] usually demonstrate greater activity and selectivity than monofunctionalized structures. In this publication we describe the synthesis of the first enantiopure planar-chiral thiourea catalysts. Pc-based bifunctional thioureas **1**–**3** are substituted to a high degree. However, only few efficient methodologies for the synthesis of highly functionalized Pcs are known.[12] The Pc-based thioureas are derived from the corresponding amino alcohols. This class of compounds is generally significant for organic chemists, and the synthesis of new amino alcohols is relevant. We utilized the planar-chiral amino alcohols in the synthesis of the first examples of new enantiopure, bifunctional planar-chiral thiourea derivatives (Figure 1, **1**–**3**). The latter were applied in organocatalytic, asymmetric transformations.

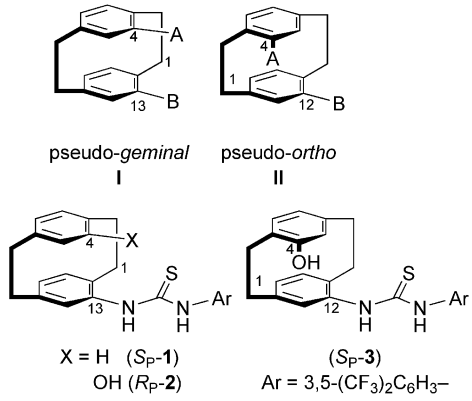

Figure 1. Selected isomers of a disubstituted [2.2]paracyclophane (**I** and **II**) and of planar-chiral thiourea derivatives for asymmetric hydrogen-bond catalysis (**1**–**3**).

Results and Discussion

Generally, thioureas can be generated through the reaction of amines with suitable isothiocyanates. Because enantiopure amines **4**–**6** (Figure 2) are not accessible from the chiral pool, optical resolution must be applied. For the installation of the individual substitution pattern of the Pc derivatives, different synthetic strategies are required: Although the same functional groups are located on the planar-chiral scaffold, the synthesis of isomeric thiourea derivatives R_P-**2** and S_P-**3** demand distinct synthetic pathways.

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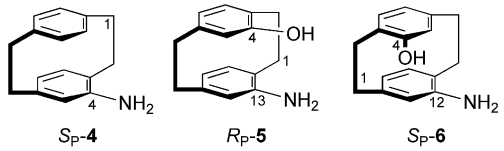
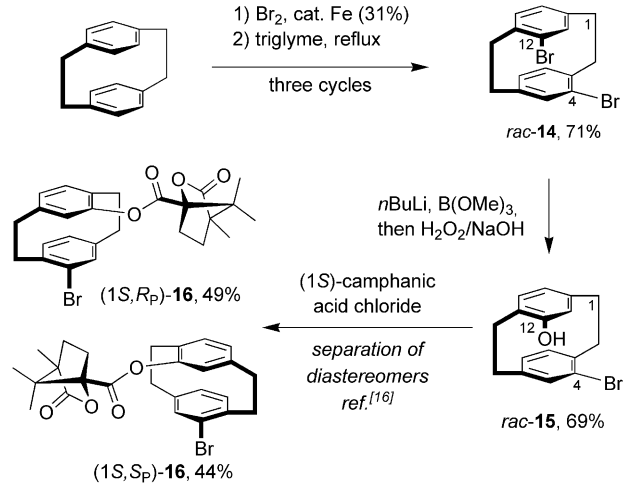


Figure 2. Planar-chiral amines **4**–**6** as precursors for thioureas.

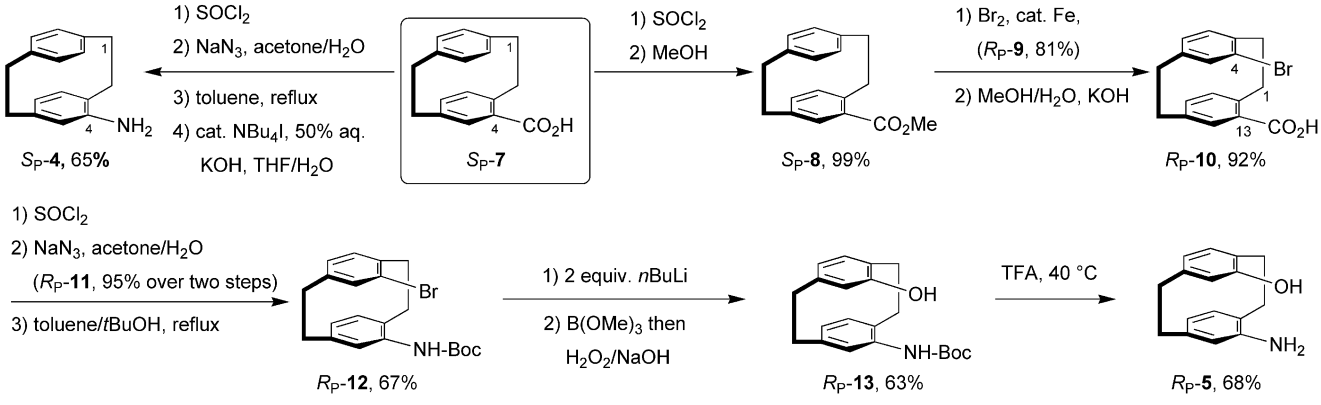
Amines S_P-**4** and R_P-**5** can be derived from a common carboxylic acid intermediate (i.e., S_P-**7**, Scheme 1). Carboxylic acids can be converted into the corresponding amines through Curtius rearrangement, making Pc carboxylic acid **7** a valuable starting material.[13] Additionally, readily accessible *rac*-**7** can be resolved in large quantities through cocrystallization with a chiral amine.[13b] Enantiopure monofunctional amine S_P-**4** was synthesized in 65% yield starting from enantiopure Pc carboxylic acid (S_P-**7**, Scheme 1), according to established procedures.[13b] This procedure only required the purification of (S_P)-4-amino[2.2]paracyclophane (S_P-**4**). However, the synthesis of amino alcohol R_P-**5** relies on the selective functionalization of position 13. It has been demonstrated that substituents on the Pc framework – such as carboxylic acids, esters, and nitro groups, allow regioselective electrophilic aromatic substitution in the pseudo-*geminal* position. This position was accessed through the regioselective bromination of methyl ester S_P-**8**,[14] obtained through the reaction of the acid chloride with methanol. The saponification of resulting bromo ester R_P-**9**[14] generated bromo carboxylic acid S_P-**10**, which then served as a precursor for the Curtius rearrangement (Scheme 1). The thermally generated isocyanate (from R_P-**11**) was trapped by *tert*-butyl alcohol to obtain Boc-protected (Boc = *tert*-butoxycarbonyl) amine R_P-**12** in 67% yield over two steps. The Boc group facilitates the selective metalation of the second aromatic ring by halogen–lithium exchange. The resultant lithiated species was treated with trimethylborate. The subsequent oxidative workup produced Boc-protected amino alcohol R_P-**13** in 63% yield. The protecting group was removed by trifluoroacetic acid in dichloromethane at 40 °C and free amino alcohol R_P-**5** was isolated in 68% yield.

Generally, the pseudo-*ortho* position in the Pc framework is difficult to access. The dibromination of Pc (31% yield) and subsequent isomerization of the predominant pseudo-*para* dibromo isomer (4,16-dibromo[2.2]paracyclophane) to the 4,12-dibromo[2.2]paracyclophane (*rac*-**14**, 71%)[15] offers a potential synthetic approach towards the desired substitution pattern. Thereafter, dibromide *rac*-**14** was converted into bromo alcohol *rac*-**15**, which was resolved through the separation of the diastereomeric esters of (1*S*)-camphanic acid.[16] Diastereomeric esters (1*S*,R_P)-**16** and (1*S*,S_P)-**16** were obtained as white crystalline solids in 49 and 44% yield, respectively, after column chromatography (Scheme 2). As depicted in Figure 3, the (1*S*,R_P)-**16** diastereomer was crystallized and subjected to X-ray crystal-structure analysis.[17]



Scheme 2. Optical resolution of *rac*-**15**.

The unit cell consists of three independent molecules. In contrast to the (1*S*,S_P)-diastereomer, previously presented in the literature, which exhibits an orthorhombic elemental cell, the compound crystallizes within the monoclinic space group $P2_1$ (No. 4). Its structure reveals the absolute stereochemistry of 1*S*,R_P and the pseudo-*ortho* orientation of the



Scheme 1. Synthesis of S_P-**4** and R_P-**5**.

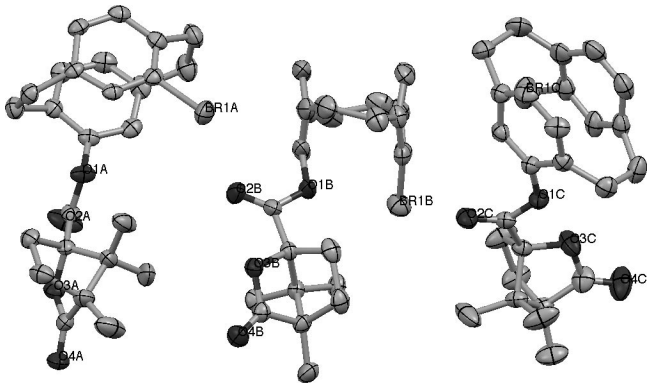
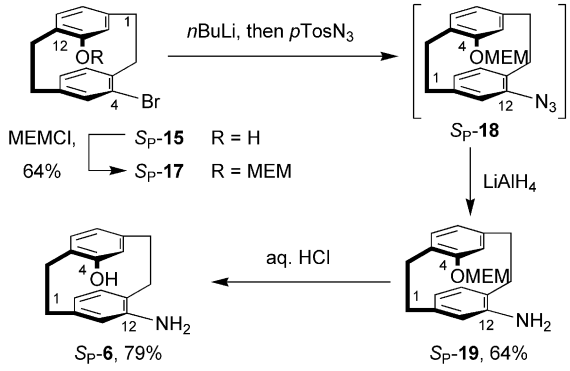


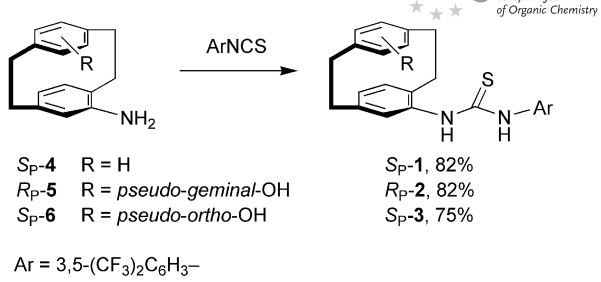
Figure 3. Representation of the X-ray crystal structure of (1*S*,*R*P)-**16** (the hydrogen atoms are omitted for clarity).[18]

bromide atom with respect to the ester functionality. The distance between the two heteroatoms in the 4- and 12-positions is 4.183 Å, a significantly larger distance than for substituents in the 4- and 13-positions (3.009 Å, see Supporting Information). This seemingly indicates that the difference in distance between the two functional groups should lead to varying activity and/or selectivity in enantioselective organic transformations Solvolysis of ester *R*P-**16** with potassium hydroxide furnished enantiopure bromo alcohol *R*P-**15** quantitatively (96%). To establish the amino functionality[9a,19] through halogen–lithium exchange and reaction with a nitrogen electrophile, it was necessary to protect the hydroxy group[20] as MEM ether *R*P-**17** (64%) (MEM = methoxyethoxymethylene; Scheme 3). After treatment of *R*P-**17** with *n*-butyllithium, the metalated [2.2]paracyclophane derivative was treated with tosyl azide to generate 13-azido-substituted ether *S*P-**18**. The latter was subsequently reduced to amine *S*P-**19** in 64% yield. Deprotection of the hydroxy group produced 12-amino-4-hydroxy[2.2]paracyclophane (*S*P-**6**, 79%).



Scheme 3. Synthesis of pseudo-*ortho* amino alcohol *S*P-**6** (*p*Tos = *p*-toluenesulfonyl).

Enantiopure amines *S*P-**4**, *R*P-**5**, and *S*P-**6** were converted into enantiopure thiourea derivatives *S*P-**1**, *R*P-**2**, and *S*P-**3** through reaction with 3,5-bis(trifluoromethyl)phenyl isothiocyanate in excellent yields (75–82%, Scheme 4).



Scheme 4. Synthesis of enantiopure planar-chiral thioureas **1**–**3** [Ar = 3,5-bis(trifluoromethyl)phenyl].

We were able to obtain single crystals suitable for X-ray structure determination of *rac*-**1** (Figure 4, *rac*-**1** was obtained from amine *rac*-**4**).

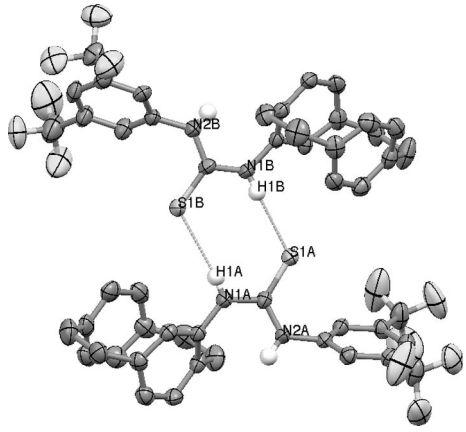
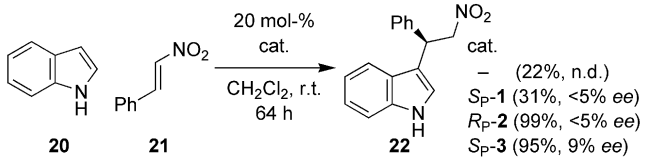


Figure 4. X-ray crystal structure of *rac*-**1**. (peripheral hydrogen atoms and one molecule of chloroform are omitted for clarity).[21]

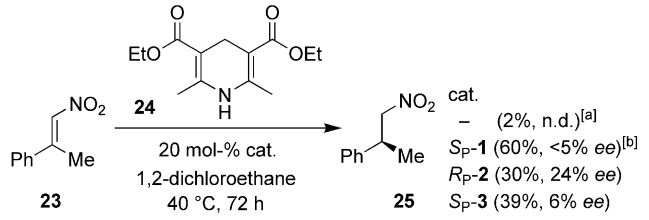
Analysis reveals the presence of both enantiomers in the elemental cell. The two thiourea moieties exhibit *s-cis*, *trans* conformation, resulting in a hydrogen-bonding interaction between the two enantiomeric structures (N–H···S distances of 2.542 and 2.688 Å).[22] These findings encouraged us to investigate the potential of thioureas **1**–**3** as hydrogen-bond donors in organic transformations.

Designed enantiopure thioureas *S*P-**1**, *R*P-**2**, and *S*P-**3** were employed in asymmetric transformations. We selected two reactions that require the activation of both reactants to enable a selective process. Reactions meeting these requirements are the asymmetric Friedel–Crafts alkylation of indole[23] and the transfer hydrogenation of nitroolefins.[24] Both reactions are assumed to involve the binding of the nitroolefin to the thiourea moiety, while the corresponding heterocycle is bound simultaneously to the catalyst through an additional hydrogen bond.[23] The OH groups in the structure of the catalysts are known to be beneficial for a selective process, encouraging us to apply planar-chiral thioureas **1**–**3** to these reactions. Firstly, we focused on the organocatalytic Friedel–Crafts alkylation reaction. The reaction of indole (**20**) with *trans*-β-nitrostyrene (**21**) yielded 3-alkylindole **22** (Scheme 5).



Scheme 5. Friedel–Crafts alkylation of indole (**20**) and *trans*-β-nitrostyrene (**21**).

As hypothesized, bifunctional hydroxy-substituted thioureas R_P-**2** and R_P-**3** catalyzed the reaction efficiently (99 and 95% yield, respectively), whereas monofunctional thiourea S_P-**1** generated the product in lower yield (31%). Although bifunctional thioureas R_P-**2** and R_P-**3** performed very well in this reaction, the stereoselectivity was very low (for more experiments see the Supporting Information). As a second application of the planar-chiral thiourea catalysts, we investigated the asymmetric transfer hydrogenation of nitroolefin **23** (Scheme 6).



Scheme 6. Organocatalytic asymmetric transfer hydrogenation of **23** with Hantzsch ester **24**
[a] reaction performed in toluene; [b] reaction was carried out at 60 °C.

The reaction was catalyzed by new planar-chiral thioureas **1**–**3**. Monofunctional hydrogen-bond catalyst S_P-**1** yielded nitroalkane **25** in 60% yield as a racemic mixture. Whereas pseudo-*ortho*-substituted catalyst S_P-**3** furnished hydrogenated product **25** as racemic material in 39% yield, isomeric pseudo-*geminal*-substituted thiourea R_P-**2** yielded the product in 30% yield and 24% enantiomeric excess. In summary, these results illustrate the activity of the new hydrogen-bond catalysts in organic transformations. Monofunctional thiourea S_P-**1** catalyzed the transfer hydrogenation of nitroolefins in good yield but with no selectivity. This might be a result of the interconversion of the conformations of the thiourea moiety (*s-cis*, *trans*/*s-cis*, *cis*/*s-trans*, *trans*). The hydroxy functionality proves to be crucial for enhanced activity in the Friedel–Crafts alkylation and for stereoinduction in the transfer hydrogenation. Pseudo-*geminal* functionalized catalyst R_P-**2** is able to induce stereoselectivity in the transfer hydrogenation of nitroolefins, whereas pseudo-*ortho* functionalized catalyst S_P-**3** produces racemic material. Not only is the second functionality itself significant for the transformation but its orientation to the thiourea moiety is also crucial. The pseudo-*geminal* substituent might stabilize a thiourea conformation, which gives rise for a more selective transformation. The potential of planar-chiral catalysts will be explored in successive organocatalytic reactions with pseudo-*geminal*-substituted thioureas.

Conclusions

In conclusion, we have developed the synthesis of the first enantiopure planar-chiral thioureas, all of which were applied in asymmetric organocatalytic transformations. We demonstrated that the planar-chiral [2.2]paracyclophane scaffold is suitable to accommodate the thiourea and hydroxy moieties to furnish bifunctional hydrogen-bonded catalysts. Isomeric bifunctional thiourea catalysts R_P-**2** and S_P-**3** display distinct selectivity, while conserving their activity. This alteration in selectivity can be explained by the change in orientation of the second functionality in the bifunctional catalyst structures. This discrepancy serves as a step towards the rational design of catalysts and will be further investigated with different [2.2]paracyclophane derivatives.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, full characterization of new compounds, NMR spectra, and HPLC traces.

Acknowledgments

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[1] a) T. J. Colacot, *Chem. Rev.* **2003**, *103*, 3101–3118; b) C. Bolm, K. Muniz, *Chem. Soc. Rev.* **1999**, *28*, 51–59; c) R. L. Haltermann, A. Togni, *Metallocenes*, Wiley-VCH, Weinheim, **1998**.
[2] a) R. P. Wurz, *Chem. Rev.* **2007**, *107*, 5570–5595; b) G. C. Fu, *Acc. Chem. Res.* **2006**, *39*, 853–860.
[3] a) R. G. Arrayas, J. Adrio, J. C. Carretero, *Angew. Chem.* **2006**, *118*, 7836–7878; *Angew. Chem. Int. Ed.* **2006**, *45*, 7674–7715; b) A. Togni, *Angew. Chem.* **1996**, *108*, 1581–1583; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1475–1477; c) A. Togni, T. Hayashi, *Ferrocenes: Homogeneous Catalysis, Organic Synthesis Materials Science*, Wiley-VCH, Weinheim, **1994**.
[4] S. E. Gibson, J. D. Knight, *Org. Biomol. Chem.* **2003**, *1*, 1256–1269.
[5] a) M. Kreis, C. J. Friedmann, S. Bräse, *Chem. Eur. J.* **2005**, *11*, 7387–7394; b) P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante, P. J. Reider, *J. Am. Chem. Soc.* **1997**, *119*, 6207–6208; c) K. Rossen, P. J. Pye, A. Maliakal, R. P. Volante, *J. Org. Chem.* **1997**, *62*, 6462–6463.
[6] a) A. Fürstner, M. Alcarazo, H. Krause, C. W. Lehmann, *J. Am. Chem. Soc.* **2007**, *129*, 12676–12677; b) T. Focken, J. Rudolph, C. Bolm, *Synthesis* **2005**, 429–436; c) C. Bolm, T. Focken, G. Raabe, *Tetrahedron: Asymmetry* **2003**, *14*, 1733–1746; d) Y. D. Ma, C. Song, C. Q. Ma, Z. J. Sun, Q. Chai, M. B. Andrus, *Angew. Chem.* **2003**, *115*, 6051–6054; *Angew. Chem. Int. Ed.* **2003**, *42*, 5871–5874; e) C. Bolm, M. Kesselgruber, G. Raabe, *Organometallics* **2002**, *21*, 707–710.
[7] D. C. Braddock, I. D. MacGilp, B. G. Perry, *Adv. Synth. Catal.* **2004**, *346*, 1117–1130.
[8] a) P. I. Dalko, *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wiley-VCH, Weinheim, **2007**; b) H. Gröger, A. Berkessel, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**.
[9] a) P. M. Pihko, *Hydrogen Bonding in Organic Synthesis*, Wiley-VCH, Weinheim, **2009**; b) Z. G. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; c) A. G. Doyle, E. N. Jacobsen,

Chem. Rev. **2007**, *107*, 5713–5743; d) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296.
[10] a) S. J. Connon, *Synlett* **2009**, 354–376; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; c) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; d) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010.
[11] J. A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666–4683; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583.
[12] a) D. Y. Antonov, V. I. Rozenberg, T. I. Danilova, Z. A. Starikova, H. Hopf, *Eur. J. Org. Chem.* **2008**, 1038–1048; b) N. V. Vorontsova, V. I. Rozenberg, E. V. Sergeeva, E. V. Vorontsov, Z. A. Starikova, K. A. Lyssenko, H. Hopf, *Chem. Eur. J.* **2008**, *14*, 4600–4617; c) R. Gleiter, H. Hopf, *Modern Cyclophane Chemistry*, Wiley-VCH, Weinheim, **2004**; d) B. König, B. Knieriem, K. Rauch, A. de Meijere, *Chem. Ber.* **1993**, *126*, 2531–2534; e) F. Vögtle, *Cyclophan-Chemie*, Teubner Verlag, Stuttgart, **1990**; f) H. Hopf, *Org. Synth.* **1981**, *60*, 41–44.
[13] a) G. Ricci, R. Ruzziconi, E. Giorgio, *J. Org. Chem.* **2005**, *70*, 1011–1018; b) H. Falk, P. Reichroh, K. Schlögl, *Tetrahedron* **1970**, *26*, 511–527; c) D. J. Cram, N. L. Allinger, *J. Am. Chem. Soc.* **1955**, *77*, 6289–6294.
[14] a) A. Marchand, A. Maxwell, B. Mootoo, A. Pelter, A. Reid, *Tetrahedron* **2000**, *56*, 7331–7338; b) H. J. Reich, D. J. Cram, *J. Am. Chem. Soc.* **1969**, *91*, 3505–3516.
[15] L. Bondarenko, I. Dix, H. Hinrichs, H. Hopf, *Synthesis* **2004**, 2751–2759.
[16] R. Zhuravsky, Z. Starikova, E. Vorontsov, V. Rozenberg, *Tetrahedron: Asymmetry* **2008**, *19*, 216–222.
[17] The (1*S*,S_P)-**14** diastereomer was analyzed by X-ray crystal structure analysis by Rozenberg. Please see ref.[16]
[18] Data sets were collected with a Nonius Kappa CCD diffractometer. Programs used: data collection COLLECT (B. V. Nonius, 1998), data reduction Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326), absorption correction Denzo (Z. Otwinowski, D. Borek, W. Majewski, W. Minor, *Acta Crystallogr., Sect. A* **2003**, *59*, 228–234), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473), structure refinement SHELXL-97 (G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122), graphics XP (BrukerAXS, 2000). CCDC-754553 (for 1*S*,R_P-**16**) and -754552 (for *rac*-**1**) 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. Full details of the X-ray crystal structure 1*S*,R_P-**16** can be found in the Supporting Information.
[19] B. Qu, Y. D. Ma, Q. S. Ma, X. Liu, F. Y. He, C. Song, *J. Org. Chem.* **2009**, *74*, 6867–6869.
[20] We were not able to convert S_P-**15** into the azide/amine by lithiation or Hartwig–Buchwald coupling.
[21] Full details of the X-ray crystal structure of *rac*-**1** can be found in the Supporting Information.
[22] G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, New York, **1997**.
[23] R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem.* **2005**, *117*, 6734–6737; *Angew. Chem. Int. Ed.* **2005**, *44*, 6576–6579.
[24] a) N. J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 8976–8977; b) J. W. Yang, M. T. H. Fonseca, B. List, *Angew. Chem.* **2004**, *116*, 6829–6832; *Angew. Chem. Int. Ed.* **2004**, *43*, 6660–6662.

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