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Chiral and Achiral Basket-Handle Porphyrins: Short Synthesis and Stereostructures of These Versatile Building Blocks

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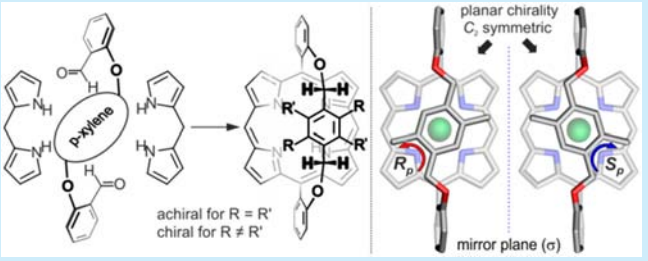
Supporting Information

ABSTRACT: Both, chiral and achiral basket-handle porphyrins were synthesized via a short, reliable, and efficient route in multigram quantities. Standard synthetic protocols such as metalation of the macrocycle, halogenation, and borylation of the porphyrin core or alkyl- and arylation with lithium organyls were successfully adapted. The planar-chiral representatives were resolved into their enantiomers, whose absolute configurations were determined by comparison of experimental CD spectra with TDCAM-B3LYP calculated ones.



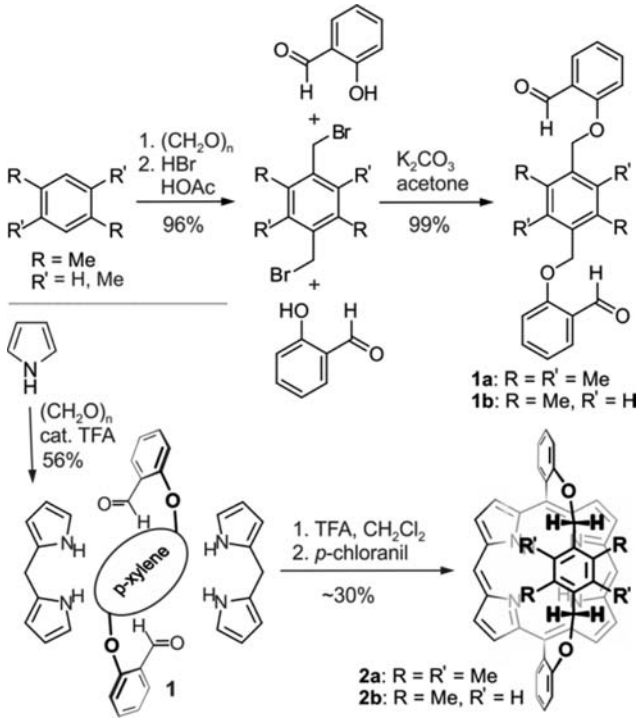
Over the past decades a plethora of porphyrin-based systems with tailor-made properties have been described. Most of these advances were made possible by the introduction of reliable yet flexible synthetic protocols that allowed a wide range of structural modifications of the porphyrin building blocks. Often the construction of defined three-dimensional geometries is of great importance, but the high symmetry that is inherent to the D_{4h}-symmetric tetrapyrrole core creates problems, since the two faces of the porphyrin are usually homo- or enantiotopic and, thus, not distinguishable.[1] Porphyrins have therefore been "capped" to block one side of the porphyrin. Due to their stereostructure, such systems have often been called basket-handle porphyrins (BHPs).[2−6] Although there are several examples of such structures, no systematic investigation on the potential of these systems as synthetic building blocks has been made so far.

We herein describe a short and reliable route to BHPs starting from very simple, commercially available materials. Most importantly our BHPs not only show interesting structural features but also offer a great variety of potential further synthetic modifications.

Since 5,15-diarylporphyrins with no further *meso*- or *β*-substitution are widely used as primary building blocks in the construction of highly complex porphyrin systems,[7−10] we tried to design a structure very similar to such 5,15-diarylporphyrins. Previous work on BHPs had often suffered from various disadvantages, which prohibited BHPs from becoming valuable, general building blocks in porphyrin chemistry. These include high numbers of synthetic steps,[2] low yields in the preparation of the strap moiety, and the condensation to the porphyrin,[11−15] poor solubility,[12] and only low-scale reactions in high dilution.[5] However, limitations for subsequent synthetic modifications are the biggest problem.

Our route delivered the BHPs in only four steps, with the longest linear sequence consisting of three reactions. All required materials were available in bulk quantities at low price (Scheme 1). The synthesis of the strap dialdehyde **1** gave almost quantitative yields, and dipyrrylmethane was easily prepared by well-established methods.[16] Under optimized

Scheme 1. From Bulk Chemicals to Basket-Handle Porphyrins



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Lindsey conditions (0.2 M in dichloromethane, 0.2% TFA, then *p*-chloranil)[17] the 2 + 2 condensation of the strap dialdehyde **1** with dipyrrylmethane gave the BHP **2** (Scheme 1). Isolation and purification procedures were similar to those of known porphyrins. After oxidation of the intermediate porphyrinogen with *p*-chloranil, NEt_3 was added and a large amount of the solvent was evaporated. Filtration over a plug of silica eliminated polar side products, providing a purple solution. After concentration, precipitation with MeOH gave analytically pure, purple crystals, without the need for further chromatographic purification. The yields varied around 28−34%, in rare cases even over 40%. Changing the conditions toward higher dilution of the reactants had no influence on the product yield. The reaction was routinely done at a 1-L scale, which delivers over 2 g of **1** in a single run. The BHPs are soluble in dichloromethane, chloroform, THF, and toluene for further reactions. The condensation conditions developed by Osuka's group (0.2 M in acetonitrile, 0.1% trichloroacetic acid, then *p*-chloranil),[3] which were optimized for similar systems, were not suitable here, because the BHPs were formed in low yields only (5−10%). Under Adler−Longo conditions (reactants in refluxing acetic or propionic acid) only trace amounts of the desired products were formed.[12,18]

With large quantities of the BHPs in hand, we explored the reactivity of these systems. First we investigated the complexation properties of the porphyrin ligand. Metalation with standard protocols[19] was successful for Ni(II), Zn(II), Pd(II), Cu(II), and Mg(II). All of the metalloporphyrins are stable, which is remarkable for magnesium, since magnesium porphyrins are usually very sensitive and do easily lose the coordinated Mg(II) ion.[20]

Consequently demetalation is almost impossible under acidic, basic, or reductive conditions. Only Mg(II) can be removed by stirring a chloroform solution of the Mg-BHP in chloroform/TFA. In all other cases no demetalation was observed before decomposition occurred. This high kinetic stability of the metal complexes is due to the steric shielding caused by the strap, preventing the classical protolytic demetalation due to the steric congestion.[19] There are only three examples of a demetalation of BHPs, but in these cases the strap is sterically less demanding or more flexible;[21−23] this issue is under further investigation.

By slow diffusion of MeOH into a diluted solution of **Ni-2a** in chloroform we managed to grow crystals suitable for single crystal X-ray diffraction. The crystal structure impressively shows the bent nature of the porphyrin macrocycle in the BHP (Figure 1).

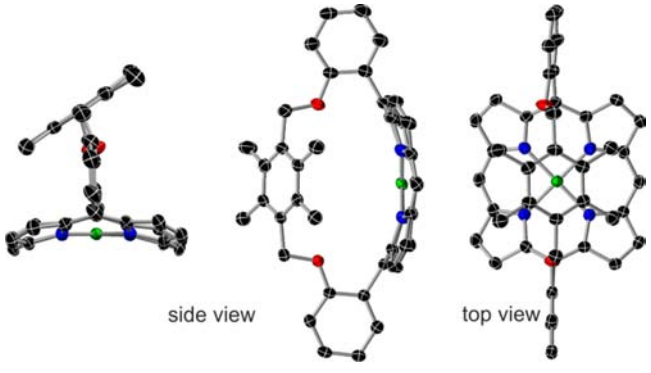

Figure 1. X-ray crystal structure of the BHP **Ni-2a**.

Previous examples of BHPs already suggested that the porphyrin macrocycle should be strongly bent, if the strap is as short as in our case.[24] The macrocycle still adopts a ruffled conformation (NSD value B_{1u} = 1.8625 Å),[25] which is typical of Ni porphyrins without the handle. One face of the porphyrin is sterically blocked by the strap, which is in close proximity to the tetrapyrrole core and of limited flexibility. This defined three-dimensional structure will be of great use when designing target molecules where a total steric shielding of one of the porphyrin faces is desired. For this purpose, the *p*-xylene strap with four methyl groups is ideal due to the rigidity and high symmetry of the resulting porphyrin.

An interesting feature of this synthetic route is the easy access to intrinsically chiral BHPs by only a minor variation in the xylene part of the strap. While four identical substituents in the *p*-xylene strap of the BHP give the C_{2v} symmetric, and thus achiral, structure **2a**, the presence of only two identical substituents located along the diagonal of the *p*-xylene moiety yield the C_2 symmetric and planar-chiral BHP **2b**. This chirality can be compared to that of *para*-cyclophanes.[26] Figure 2 shows

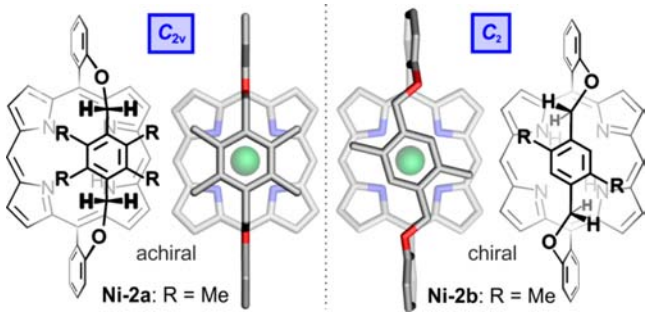

Figure 2. Natta projections and B97-D3/def2-TZVP-optimized (symmetry constraint) structures of **Ni-2**.

the structures of both the C_{2v} and the C_2 case, as idealized Natta projections and the B97-D3/def2-TZVP-optimized minimum structures of **Ni-2**. While searching for protocols for the synthesis of BHPs we found examples of such systems in the literature which we expected to be chiral,[3,27,28] but to the best of our knowledge this property has never been discussed in the literature.[29]

The C_2 symmetric compounds were synthesized in a racemic form under identical conditions as the achiral BHPs. Their chiral nature is easily noticed by ^{1}H NMR spectroscopy, where the methylene protons of the strap are diastereotopic and therefore distinguishable. The pair of enantiomers of **Ni-2b** was resolved by HPLC on a chiral phase, and online CD spectra were measured in the stopped-flow mode. Assignment of the absolute configuration was done by comparison of experimental CD spectra with results from quantum-chemical CD calculations (Figure 3). The shortness and size of the strap prohibits rotation of it around the porphyrin macrocycle (rope skipping) as well as rotation within itself, and therefore the enantiomers are conformationally very stable and cannot be racemized without thermal decomposition.

The CD curve of **Ni-2b** shows mainly one couplet at 410 nm (Soret band region); all other CD effects are negligible, and thus the CD investigations were restricted to a wavelength region above 350 nm and below 500 nm. A conformational analysis (B97-D3/def2-TZVP) of the arbitrarily chosen R_p-configured **Ni-2b** gave only one energetically relevant conformer. A subsequent TD CAM-B3LYP/def2-SVP calculation

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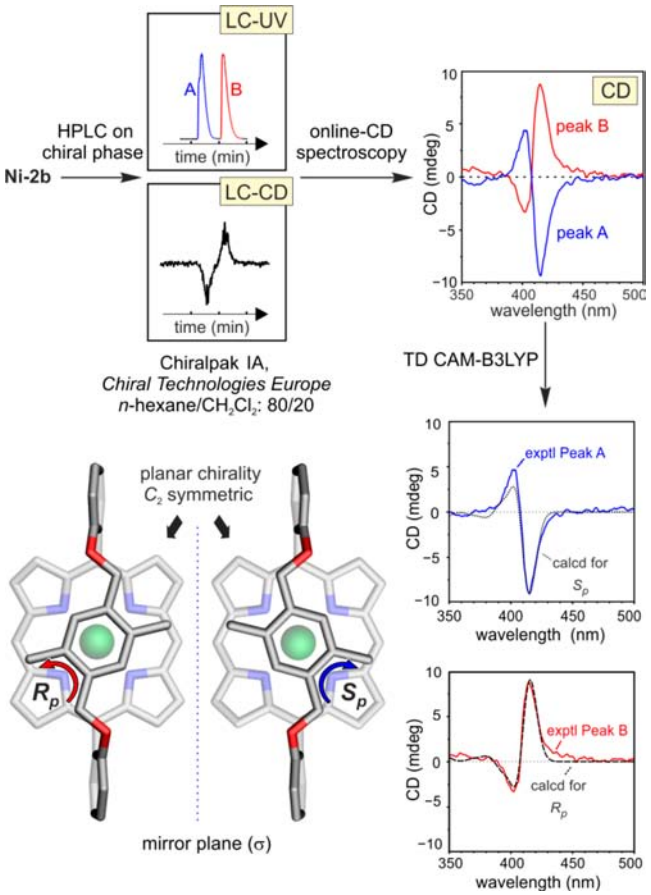


Figure 3. Determination of the absolute configuration of a chiral BHP by online CD spectroscopy in combination with quantum-chemical calculations (σ = 0.08 eV, UV shift of 47 nm).

delivered a CD curve that almost perfectly matched the CD spectrum of the slower eluting enantiomer, which thus has the R_p configuration (enantiomeric similarity index[30] Δ_{ESI} = 98%). Consequently, the calculated spectrum of the S_p configuration fits the experimental curve of the faster eluting enantiomer (Δ_{ESI} = 96%).

Of great interest was the synthetic chemical modification of the BHPs. Not only 5,15-diarylporphyrins but also 5,10,15-triarylporphyrins and 5,10,15,20-tetraarylporphyrins have widely been used as synthetic building blocks.[31,32] Tri- and tetraaryl analogs of our BHP (Figure 4) can easily be synthesized by variation of the respective dipyrrylmethanes. 5-Aryldipyrrylmethanes yield tetraaryl-like BHPs, while a mixture of 5-substituted and unsubstituted dipyrrylmethanes gives the statistical mixture of di-, tri-, and tetraaryl BHPs.

Alternatively *meso*-substitution was also achieved after the condensation step. Our BHPs can be reacted with lithium organyls according to the protocol of Senge et al.[33] Both aryl and alkyl substituents were successfully introduced at free *meso*-positions (see Figure 4).

The methods described above allow the design of a great variety of BHPs regarding their *meso*-substitution pattern and metal coordination. With such a plethora of building blocks imaginable, the next step was to functionalize the BHPs with reactive groups. First efforts to introduce bromine at a free *meso*-position were not successful and only yielded decomposition products under the commonly used conditions[34] (chloroform solution, pyridine as a base, NBS as the bromine source). After trying several different conditions we found that it is crucial to attempt the reaction without any base. Bromination of **2** with 2 equiv of NBS yielded the *meso*-brominated product **3** within minutes and with almost quantitative yields (Scheme 2). Thus, key intermediates for various transition metal catalyzed cross-coupling reactions are easily accessible.

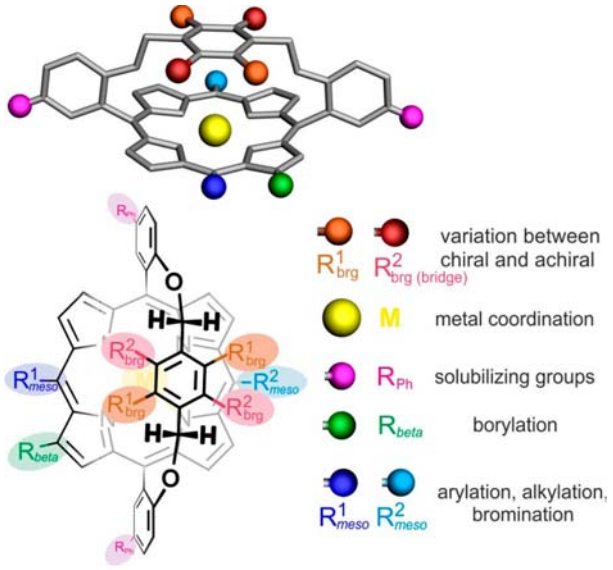
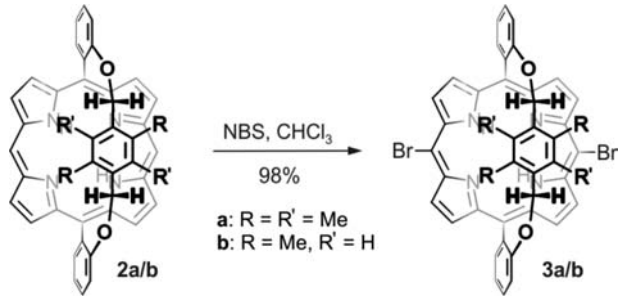


Figure 4. Possible sites for modification of the BHPs.

Scheme 2. *meso*-Bromination of BHP 2



The availability of complementary, β-functionalized porphyrin building blocks is of great importance, too.[35] We therefore explored the compatibility of our BHPs with the selective β-borylation by sterically controlled Ir-catalyzed C−H activation, as established by Osuka's group.[10] BHP **2** can be selectively borylated using previously reported conditions, if the *meso*-phenyl is sterically blocked with a 4-*tert*-butyl group. Then the reaction is possible only at the β-positions and all products from monoborylation to complete borylation are formed (Scheme 3). These building blocks open up yet another path to design complex architectures from BHPs.

Overall our BHPs offer a wide variety of potential modifications. The structures in Figure 4 show the various sites for modifications.

In summary, we have described a short and efficient route to BHPs, which starts from bulk chemicals and involves only simple synthetic transformations. The potential of our BHPs as versatile building blocks was demonstrated by facile subsequent modifications, such as metalation, derivatization, and functionalization in both β- and *meso*-positions. Our synthetic approach

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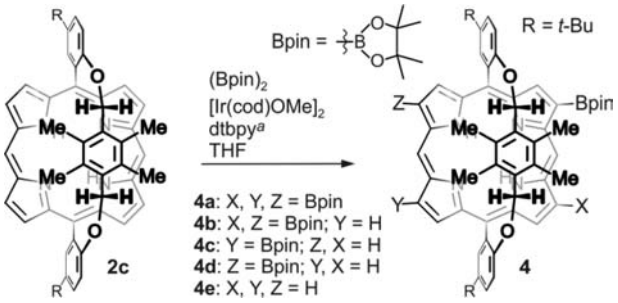
Scheme 3. Ir-Catalyzed Direct β-Borylation of BHPs



[a]dtbpy = 4,4′-*tert*-butyl-butyl-2,2′-dipyridyl.

offers access to C_{2v} (achiral) and C_2 symmetric (chiral) structures. In this case, the planar chirality is induced by the strap moiety and therefore intrinsic and independent of any structural changes. The chiral representatives were resolved into their enantiomers, and the absolute configuration was successfully established.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data for all new compounds, computational details, crystallographic data, and CIF information for **Ni-2a** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Vicente, M. d. G. H.; Smith, K. M. *Curr. Org. Synth.* **2014**, *11*, 3.
(2) Wytko, J. A.; Graf, E.; Weiss, J. *J. Org. Chem.* **1992**, *57*, 1015.
(3) Osuka, A.; Kobayashi, F.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1213.
(4) Jaquinod, L.; Prevot, L.; Fischer, J.; Weiss, R. *Inorg. Chem.* **1998**, *37*, 1142.
(5) Takeuchi, M.; Fujikoshi, C.; Kubo, Y.; Kaneko, K.; Shinkai, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 5494.
(6) Wang, Q. M.; Bruce, D. W. *Tetrahedron Lett.* **1996**, *37*, 7641.
(7) Gotz, D. C. G.; Bruhn, T.; Senge, M. O.; Bringmann, G. *J. Org. Chem.* **2009**, *74*, 8005.
(8) Ryan, A.; Gehrold, A.; Perusitti, R.; Pintea, M.; Fazekas, M.; Locos, O. B.; Blaikie, F.; Senge, M. O. *Eur. J. Org. Chem.* **2011**, *2011*, 5817.
(9) Sugita, N.; Hayashi, S.; Hino, F.; Takanami, T. *J. Org. Chem.* **2012**, *77*, 10488.
(10) Hata, H.; Shinokubo, H.; Osuka, A. *J. Am. Chem. Soc.* **2005**, *127*, 8264.
(11) Zhou, Z.; Shen, M.; Cao, C.; Liu, Q.; Yan, Z. *Chem.—Eur. J.* **2012**, *18*, 7675.
(12) Zhou, Z.; Cao, C.; Liu, Q.; Jiang, R. *Org. Lett.* **2010**, *12*, 1780.
(13) Fazio, M. A.; Durandin, A.; Tkachenko, N. V.; Niemi, M.; Lemmetyinen, H.; Schuster, D. I. *Chem.—Eur. J.* **2009**, *15*, 7698.
(14) Collman, J. P.; Decreau, R. A.; Costanzo, S. *Org. Lett.* **2004**, *6*, 1033.
(15) Shao, X.-B.; Jiang, X.-K.; Wang, X.-Z.; Li, Z.-T.; Zhu, S.-Z. *Tetrahedron* **2003**, *59*, 4881.
(16) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391.
(17) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827.
(18) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.
(19) (a) Buchler, J. W. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. *1*, p 389. (b) Lavallee, D. K. *Coord. Chem. Rev.* **1985**, *61*, 55. (c) Lavallee, D. K. *Comments Inorg. Chem.* **1986**, *5*, 155.
(20) Lindsey, J. S.; Woodford, J. N. *Inorg. Chem.* **1995**, *34*, 1063.
(21) Le Gac, S.; Najjari, B.; Dorcet, V.; Roisnel, T.; Fusaro, L.; Luhmer, M.; Furet, E.; Halet, J.-F.; Boitrel, B. *Chem.—Eur. J.* **2013**, *19*, 11021.
(22) Melin, F.; Choua, S.; Bernard, M.; Turek, P.; Weiss, J. *Inorg. Chem.* **2006**, *45*, 10750.
(23) Fang, Z.; Breslow, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5463.
(24) Zaitseva, S. V.; Zdanovich, S. A.; Koifman, O. I. *Russ. J. Gen. Chem.* **2007**, *77*, 1275.
(25) Shelnutt, J. A.; Song, X.-Z.; Ma, J.-G.; Jia, S.-L.; Jentzen, W.; Medforth, C. J. *Chem. Soc. Rev.* **1998**, *27*, 31.
(26) Gibson, S. E.; Knight, J. D. *Org. Biomol. Chem.* **2003**, *1*, 1256.
(27) Osuka, A.; Kobayashi, F.; Nagata, T.; Maruyama, K. *Chem. Lett.* **1990**, 287.
(28) Zaitseva, S. V.; Zdanovich, S. A.; Koifman, O. I. *Zh. Neorg. Khim.* **2003**, *48*, 137.
(29) (a) Hembury, G. A.; Borokov, V. V.; Inoue, Y. *Chem. Rev.* **2008**, *108*, 1. (b) Tomé, A. C.; Silva, A. M. S.; Alkorta, I.; Elguero, J. *J. Porphyrins Phthalocyanines* **2011**, *16*, 1.
(30) Bruhn, T.; Schaumlöffel, A.; Hemberger, Y.; Bringmann, G. *Chirality* **2013**, *25*, 243.
(31) Senge, M. O. *Chem. Commun.* **2011**, *47*, 1943.
(32) Bringmann, G.; Götz, D. C. G.; Gulder, T. A. M.; Gehrke, T. H.; Bruhn, T.; Kupfer, T.; Radacki, K.; Braunschweig, H.; Heckmann, A.; Lambert, C. *J. Am. Chem. Soc.* **2008**, *130*, 17812.
(33) Senge, M. O. *Acc. Chem. Res.* **2005**, *38*, 733.
(34) Chumakov, D. E.; Khoroshutin, A. V.; Anisimov, A. V.; Kobrakov, K. I. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2009**, *45*, 259.
(35) Cai, H.; Fujimoto, K.; Lim, J. M.; Wang, C.; Huang, W.; Rao, Y.; Zhang, S.; Shi, H.; Yin, B.; Chen, B.; Ma, M.; Song, J.; Kim, D.; Osuka, A. *Angew. Chem.* **2014**, *126*, 11268.

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