Helicenes

DOI: 10.1002/anie.201400474

Asymmetric Catalysis on the Nanoscale: The Organocatalytic Approach to Helicenes**

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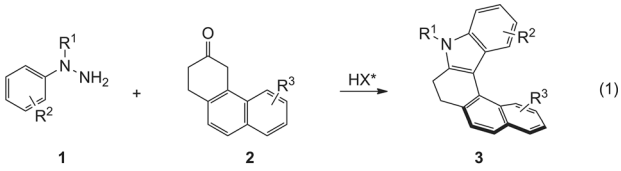
Abstract: *The first asymmetric organocatalytic synthesis of helicenes is reported. A novel SPINOL-derived phosphoric acid, bearing extended π-substituents, catalyzes the asymmetric synthesis of helicenes through an enantioselective Fischer indole reaction. A variety of azahelicenes and diazahelicenes could be obtained with good to excellent yields and enantioselectivities.*

Molecules exhibiting helical chirality have attracted significant attention in fields as diverse as catalysis, materials science, molecular self-assembly, and biology.[1] As a consequence, a number of approaches to their synthesis, especially in an enantioselective fashion, have been investigated.[1,2] In this regard, catalytic asymmetric methods are particularly attractive, but have proven to be highly challenging: unlike in common asymmetric catalysis, which builds stereogenic carbon centers, helical chirality is a phenomenon of the nanoscale, thus creating particular length-scale requirements for catalysts. Examples have previously been reported and have, in almost all cases relied on transition-metal-catalyzed [2+2+2] cycloadditions.[3] However, an expansion of the accessible structural diversity of chiral (hetero)helicenes for further investigations appeared to be desirable. Inspired by our recent development of a catalytic asymmetric Fischer indole synthesis,[4] we became interested in developing an enantioselective organocatalytic approach to helicenes. We now report a chiral Brønsted acid catalyzed asymmetric synthesis of helicenes applying the Fischer indolization.

As a planar heterocycle, indole has been part of a number of helical molecules.[5] In fact, the very first documented examples of both a pentahelicene[5a] and a hexahelicene[5b] synthesis were achieved with indole formation as the final step.

We thus hoped that, in accordance with the established mechanism of the Fischer indolization,[6] upon condensation of a phenyl hydrazine (**1**) with an appropriate polyaromatic ketone (**2**), an enantiopure Brønsted acid might promote an asymmetric [3,3] sigmatropic rearrangement to furnish enantioenriched azahelicenes of type **3** [Eq. (1)]. This approach would have the strategic advantage of starting from relatively simple, achiral starting materials. Furthermore, its modular nature would enable variation of the apical substituent (R^1) on the helicene by changing the N-substituent on the starting hydrazine, and of the terminal substituents (R^2 and R^3) by the selection of suitable hydrazines and ketones, respectively.



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Chiral Helicene Synthesis by Brønsted Acid Catalyzed Asymmetric Fischer Indolization

In light of the specific length-scale challenges associated with helical molecules, we speculated that common phosphoric acids with phenyl-derived substituents in the 3,3′-position are too short-ranged to control the enantioselectivity of such reactions. For high levels of stereocontrol, the catalyst would need extended π-substituents in the 3,3′-position that could engage in a potential π-π stacking interaction with the polyaromatic system present in the formed enehydrazine, holding the intermediate in a chiral nanometer sized pocket (Figure 1). In this way, the catalyst could induce the screw sense of the helicene.

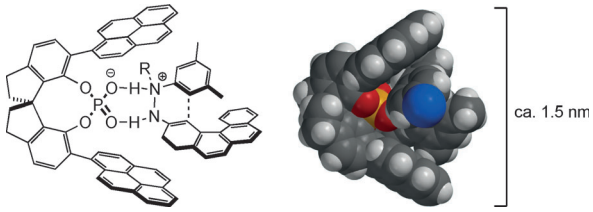

Figure 1. Concept for the asymmetric synthesis of azahelicenes using π-π stacking interactions on a nanoscale, and the 3D model of catalyst (*S*)-**5e** with the enehydrazine intermediate derived from **3a**.

Based on this concept, we synthesized various catalysts bearing extended π-substituents, such as phenanthryl, anthracenyl, and pyrenyl. These catalysts contain the features which were important for our proposal and should enable long-range control to induce enantioselectivity on the nanoscale.[7]

We began our investigations using hydrazine **1a** and polycyclic ketone **2a** as model substrates (Table 1). Different

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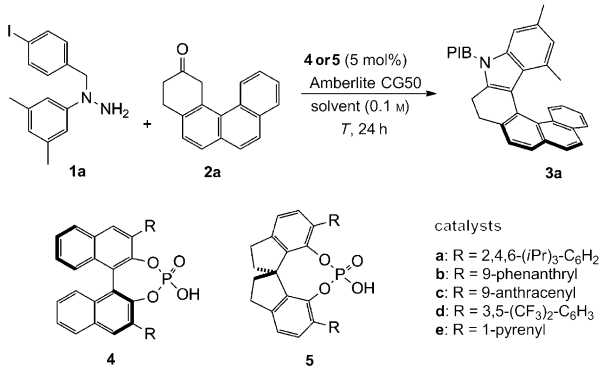
[**] We gratefully acknowledge generous support from the Max Planck Society, the European Research Council (Advanced Grant "High Performance Lewis Acid Organocatalysis, HIPOCAT"), and the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) (fellowship for C.D.F.). We also thank the members of our HPLC, NMR, MS, and crystallography departments for their support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201400474.

Table 1: Optimization of the reaction conditions.[a]



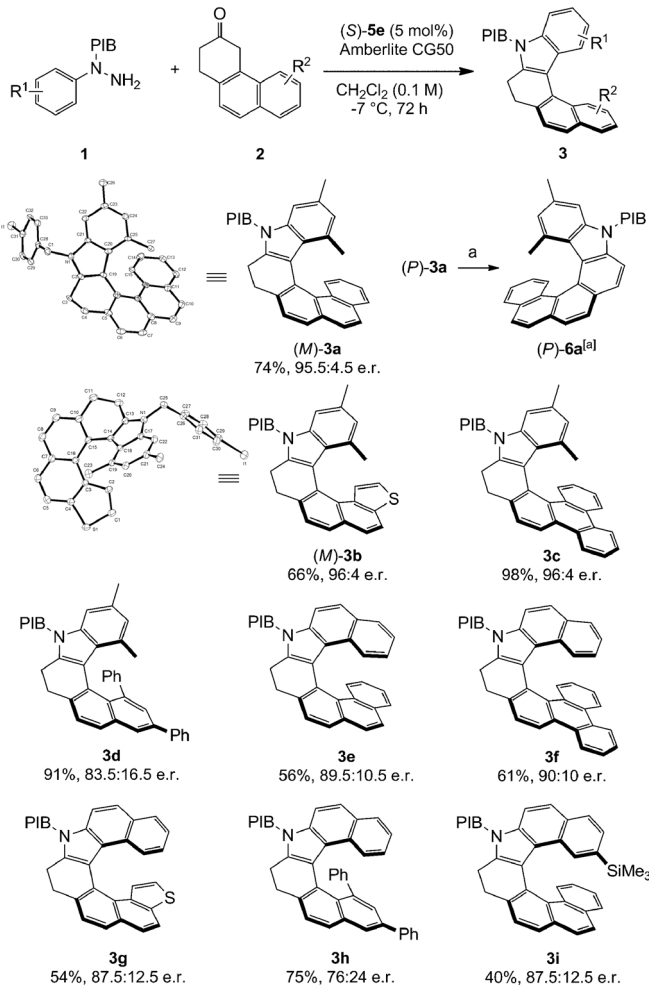
Entry	Catalyst	Solvent	T [°C]	e.r.[b]
1	**4a**	toluene	25	57:43
2	**4b**	toluene	25	68.5:31.5
3	**4c**	toluene	25	52.5:47.5
4	**4d**	toluene	25	53.5:46.5
5	**5a**	toluene	25	68.5:32.5
6	**5c**	toluene	25	82.5:17.5
7	**5c**	CH_2Cl_2	25	85.2:14.8
8	**5e**	CH_2Cl_2	25	91:9
9[c]	***5e***	CH_2Cl_2	*−7*	*95.5:4.5*

[a] Reactions were carried out on a 0.01 mmol scale with 5 mg Amberlite CG50 for 24 h (100% conversion). [b] Determined by HPLC analysis on a chiral stationary phase. [c] 3 days were required for 100% conversion.

protecting groups were screened, and the best results were obtained using a *p*-iodobenzyl group (PIB; see the Supporting Information).[4a] Various chiral phosphoric acids with different backbones were investigated.[8] Complete conversion was achieved in 24 h when reactions were carried out in toluene at room temperature. In general, SPINOL-derived catalysts[9] gave better enantioselectivities than the corresponding BINOL derivatives. Different solvents were tested, with catalyst **5c** (R = 9-anthracenyl) affording the best enantioselectivity when CH_2Cl_2 was used (Table 1, entry 7). As expected, a notable increase in the enantioselectivity of the process was observed when the π-surface of the 3,3′-substituents of the catalyst was enhanced. The use of novel catalyst **5e** bearing 1-pyrenyl substituents resulted in a promising enantiomeric ratio of 91:9 at room temperature (Table 1, entry 8), which could be improved to 95.5:4.5 by lowering the temperature to −7 °C (Table 1, entry 9).

As shown in our previous study, the weakly acidic resin Amberlite CG50, which bears carboxylic acid groups, has the remarkable ability to facilitate catalyst turnover without diminishing the level of enantioselectivity.[4] The addition of 500 mg mmol^{-1} of resin proved ideal, with higher loadings leading to decreased enantioselectivity. It is noteworthy that the reaction proceeds slowly in the absence of resin, but still with catalyst turnover (see the Supporting Information).

With the optimized conditions in hand we studied the scope of this transformation for different hydrazines and ketones (Scheme 1). Hydrazine **1a** reacted smoothly with different polycyclic ketones to give the corresponding [6]azahelicenes **3a–c** in good to excellent yields and enantioselectivities. The structure of **3a**, including its absolute configuration, was assigned unambiguously by X-ray crystallography (see the Supporting Information). This compound shows *M* helicity when the *S* enantiomer of catalyst **5e** is used and can be isolated with a high enantiomeric ratio of 95.5:4.5.

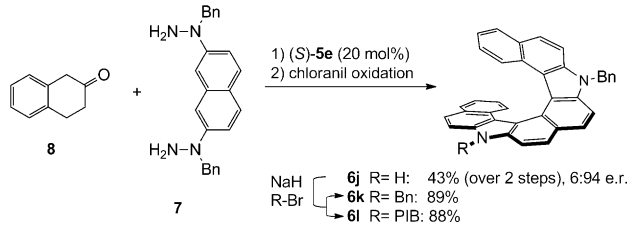


Scheme 1. Substrate scope of the azahelicene synthesis. a) Oxidation of (*P*)-**3a** (derived from (*R*)-**5e**): chloranil (5 equiv), DPP (1 equiv), $CHCl_3$, 50 °C, 5 h, 76%.

Oxidation of (*P*)-**3a**, with an excess of tetrachloro-1,4-benzoquinone (chloranil) and diphenylphosphate (DPP) readily provides polyaromatic compound (*P*)-**6a** in 76% yield. The use of a thiophene-derived ketone is also possible and gives an enantioselectivity of 96:4 for **3b**, the absolute configuration of which was also assigned by X-ray crystallography (see the Supporting Information). Even a $SiMe_3$-substituted helicene (**3i**) could be generated with a similar enantioselectivity as that observed with unsubstituted helicene **3e**.

We further became interested in extending our approach to the synthesis of diazahelicenes through a double Fischer indolization. Indeed, treating hydrazine **7** with commercially available ketone **8** led to a diazahelicene, which interestingly now bears only one benzyl group (Scheme 2).

This compound was highly sensitive to oxidation, which rendered the purification and full characterization more



Scheme 2. Synthesis of diazahelicenes **6j–l** by a double Fischer indolization, followed by oxidation and protection.

challenging than for the previous azahelicenes (Scheme 1). Thus, we decided to directly oxidize product **3j** to the polyaromatic diazahelicene **6j**. As expected, **6j** was isolated as the monobenzylated product with a good enantiomeric ratio of 6:94.[10] Following the reaction by mass spectrometry (MS) we were able to detect benzylamine, which was released during the reaction. We assume, that after the [3,3] sigmatropic rearrangement, the free enamine attacks the formed benzylimine. This imine could be stabilized by the hydrazine, the formed hydrazone, or by the indole, depending on when the benzylamine released (see the Supporting Information).[11] The selective loss of one benzyl group in the presence of catalyst **5e** allowed modifications of product **6j**, such as a benzylation to obtain the symmetrical compound **6k** or the addition of a PIB group in this position to give product **6l**. This interesting result potentially broadens the substrate scope, as other substituents could readily be introduced by this route.

We recorded the CD spectra of (*M*)-**3a**, (*P*)-**3a**, and (*P*)-**6a** to assign the helicity of our products. We found a significant agreement between the CD characteristics of our azahelicenes and those of (+)-(*P*)-[6]helicene, whose absolute configuration is known (Figure 2a).[12] In this way we could ascribe independently the *P* (dextrorotatory) and *M* (levorotatory) helicity of our products by both CD spectroscopy and X-ray crystallography.

It is known that helicenes can racemize under thermal conditions and the free energy for this process can be measured. For example, the racemization of [6]helicene has a free energy barrier of 154.5 kJ mol^{-1} at 188 °C.[13] We studied the racemization of azahelicene (*P*)-**6a**[14] by following the change in the enantiomeric ratio over different time periods at 240 °C in tetraglyme. The resulting data allowed us to calculate the racemization barrier ($\Delta G^{\ddagger}$) to be 172.2 ± 0.4 kJ mol^{-1} (Figure 2b). This value is very similar to the reported barrier of [7]helicene (175.1 kJ mol^{-1}).[13a]

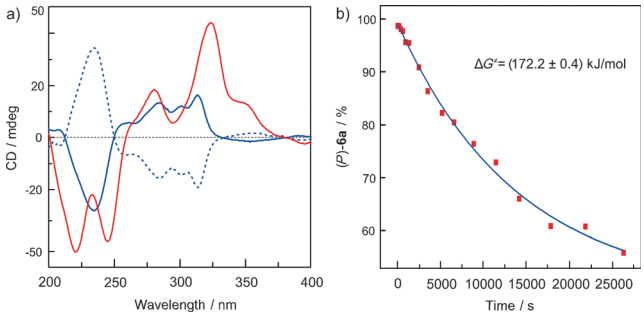


Figure 2. a) CD spectra of (*P*)-**3a** (blue line, 6.37×10^{-5} M), (*P*)-**6a** (red line, 8.87×10^{-5} M), and (*M*)-**3a** (blue dashed line, 4.07×10^{-5} M) in methanol. b) Thermal racemization of (*P*)-**6a** in tetraglyme (1 M), 240 °C.

In conclusion, we have developed a mild and powerful organocatalytic enantioselective synthesis of helicenes through catalytic asymmetric Fischer indole reactions. This approach gives access to enantioenriched azahelicenes starting from simple achiral starting materials, which allow broad substrate diversity. A new SPINOL-derived chiral phosphoric acid has been designed specifically for long-range control on a nanoscale.

Received: January 16, 2014
Published online: April 15, 2014

Keywords: Brønsted acid catalysis · Fischer indole synthesis · helicenes · organocatalysis

[1] For reviews on the synthesis and applications of helicenes, see a) M. Gingras, *Chem. Soc. Rev.* **2013**, *42*, 968–1006; b) M. Gingras, G. Félix, R. Peresutti, *Chem. Soc. Rev.* **2013**, *42*, 1007–1050; c) M. Gingras, *Chem. Soc. Rev.* **2013**, *42*, 1051–1095; d) Y. Shen, C.-F. Chen, *Chem. Rev.* **2012**, *112*, 1463–1535; e) I. G. Stará, I. Starý in *Science of Synthesis*, *Vol. 45b* (Eds.: J. S. Siegel, Y. Tobe), Thieme, Stuttgart, **2010**, pp. 885–953; f) I. Starý, I. G. Stará in *Strained Hydrocarbons* (Ed.: H. Dodziuk), Wiley-VCH, Weinheim, **2009**, pp. 166–176; g) A. Rajca, M. Miyasaka in *Functional Organic Materials* (Eds.: T. J. J. Müller, U. H. F. Bunz), Wiley-VCH, Weinheim, **2007**, pp. 547–581; h) A. Urbano, *Angew. Chem.* **2003**, *115*, 4116–4119; *Angew. Chem. Int. Ed.* **2003**, *42*, 3986–3989.

[2] a) A. Grandbois, S. K. Collins, *Chem. Eur. J.* **2008**, *14*, 9323–9329; b) A. Sudhakar, T. Katz, *J. Am. Chem. Soc.* **1986**, *108*, 179–181; c) M. C. Carreño, S. García-Cerrada, A. Urbano, *J. Am. Chem. Soc.* **2001**, *123*, 7929–7930; d) Y. Ogawa, M. Toyama, M. Karikomi, K. Seki, K. Haga, T. Uyehara, *Tetrahedron Lett.* **2003**, *44*, 2167–2170; e) M. C. Carreño, M. González-López, A. Urbano, *Chem. Commun.* **2005**, 611–613; f) I. G. Stará, Z. Alexandrová, F. Teplý, P. Sehnal, I. Starý, D. Šaman, M. Buděšínský, J. Cvačka, *Org. Lett.* **2005**, *7*, 2547–2550; g) P. Sehnal, I. G. Stará, D. Šaman, M. Tichý, J. Míšek, J. Cvačka, L. Rulíšek, J. Chocholoušova, J. Vacek, G. Goryl, M. Szymonski, I. Císařová, I. Starý, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 13169–13174; h) M. S. M. Pearson, D. R. Carbery, *J. Org. Chem.* **2009**, *74*, 5320–5325; i) J. Žádný, A. Jančařík, A. Andronova, M. Šámal, J. V. Chocholoušová, J. Vacek, R. Pohl, D. Šaman, I. Císařová, I. G. Stará, I. Starý, *Angew. Chem.* **2012**, *124*, 5959–5963; *Angew. Chem. Int. Ed.* **2012**, *51*, 5857–5861.

[3] For selected examples, see a) I. G. Stará, I. Starý, A. Kollárovic, F. Teplý, Š. Vyskočil, D. Šaman, *Tetrahedron Lett.* **1999**, *40*, 1993–1996; b) F. Teplý, I. G. Stará, I. Starý, A. Kollárovic, D. Šaman, Š. Vyskočil, P. Fiedler, *J. Org. Chem.* **2003**, *68*, 5193–5197; c) J. Caeiro, D. Peña, A. Cobas, D. Pérez, E. Guitián, *Adv. Synth. Catal.* **2006**, *348*, 2466–2474; d) K. Tanaka, A. Kamisawa, T. Suda, K. Noguchi, M. Hirano, *J. Am. Chem. Soc.* **2007**, *129*, 12078–12079; e) K. Tanaka, N. Fukawa, T. Suda, K. Noguchi, *Angew. Chem.* **2009**, *121*, 5578–5581; *Angew. Chem. Int. Ed.* **2009**, *48*, 5470–5473; f) N. Fukawa, T. Osaka, K. Noguchi, K. Tanaka, *Org. Lett.* **2010**, *12*, 1324–1327; g) T. Shibata, T. Uchiyama, Y. Yoshinami, S. Takayasu, K. Tsuchikama, K. Endo, *Chem. Commun.* **2012**, *48*, 1311–1313; h) Y. Sawada, S. Furumi, A. Takai, M. Takeuchi, K. Noguchi, K. Tanaka, *J. Am.*

Chem. Soc. **2012**, *134*, 4080 – 4083; i) A. Jančařík, J. Rybáček, K. Cocq, J. Vacek Chocholoušová, J. Vacek, R. Pohl, L. Bednárová, P. Fiedler, I. Císařová, I. G. Stará, I. Starý, *Angew. Chem.* **2013**, *125*, 10154 – 10159; *Angew. Chem. Int. Ed.* **2013**, *52*, 9970 – 9975.

[4] a) S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534 – 18537; b) A. Martínez, M. J. Webber, S. Müller, B. List, *Angew. Chem.* **2013**, *125*, 9664 – 9668; *Angew. Chem. Int. Ed.* **2013**, *52*, 9486 – 9490.

[5] a) J. Meisenheimer, K. Witte, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 4153 – 4164; b) W. Fuchs, F. Niszel, *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 209 – 217; c) F. B. Mallory, C. S. Wood, J. T. Gordon, *J. Am. Chem. Soc.* **1964**, *86*, 3094 – 3102; d) I. Pischel, S. Grimme, S. Kotila, M. Nieger, F. Vögtle, *Tetrahedron: Asymmetry* **1996**, *7*, 109 – 116; e) S. D. Dreher, D. J. Weix, T. J. Katz, *J. Org. Chem.* **1999**, *64*, 3671 – 3678; f) K. Nakano, Y. Hidehira, K. Takahashi, T. Hiyama, K. Nozaki, *Angew. Chem.* **2005**, *117*, 7298 – 7300; *Angew. Chem. Int. Ed.* **2005**, *44*, 7136 – 7138.

[6] For the original mechanistic proposal, see G. M. Robinson, R. Robinson, *J. Chem. Soc. Abstr.* **1924**, *125*, 827 – 840.

[7] Studies on the nonlinear effects are in agreement with our concept, with no nonlinear effect observed for our reaction (see the Supporting Information).

[8] For reviews on chiral phosphoric acid catalysis, see a) M. Terada, *Synthesis* **2010**, 1929 – 1982; b) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395 – 456; c) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758.

[9] SPINOL-derived phosphoric acids were independently introduced by three research groups: a) F. Xu, D. Huang, C. Han, W. Shen, X. Lin, Y. Wang, *J. Org. Chem.* **2010**, *75*, 8677 – 8680; b) I. Čorić, S. Müller, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 17370 – 17373; c) C.-H. Xing, Y.-X. Liao, J. Ng, Q.-S. Hu, *J. Org. Chem.* **2011**, *76*, 4125 – 4131.

[10] The corresponding doubly benzylated compound was only formed in trace amounts in the presence of catalyst (*S*)-**5e**.

[11] The fully debenzylated compound was not detected by MS.

[12] a) M. S. Newnam, R. S. Darlak, L. Tsai, *J. Am. Chem. Soc.* **1967**, *89*, 6191 – 6193; b) D. A. Lightner, D. T. Hefelfinger, T. W. Powers, G. W. Frank, K. N. Trueblood, *J. Am. Chem. Soc.* **1972**, *94*, 3492 – 3497.

[13] a) R. H. Martin, M. J. Marchant, *Tetrahedron* **1974**, *30*, 347 – 349; b) R. H. Martin, M. J. Marchant, *Tetrahedron Lett.* **1972**, *13*, 3707 – 3708; for computational studies, see c) R. H. Janke, G. Haufe, E.-U. Würthwein, J. H. Borkent, *J. Am. Chem. Soc.* **1996**, *118*, 6031 – 6035.

[14] Compound **3a** decomposed at 240 °C, so its corresponding racemization data were not consistent.

