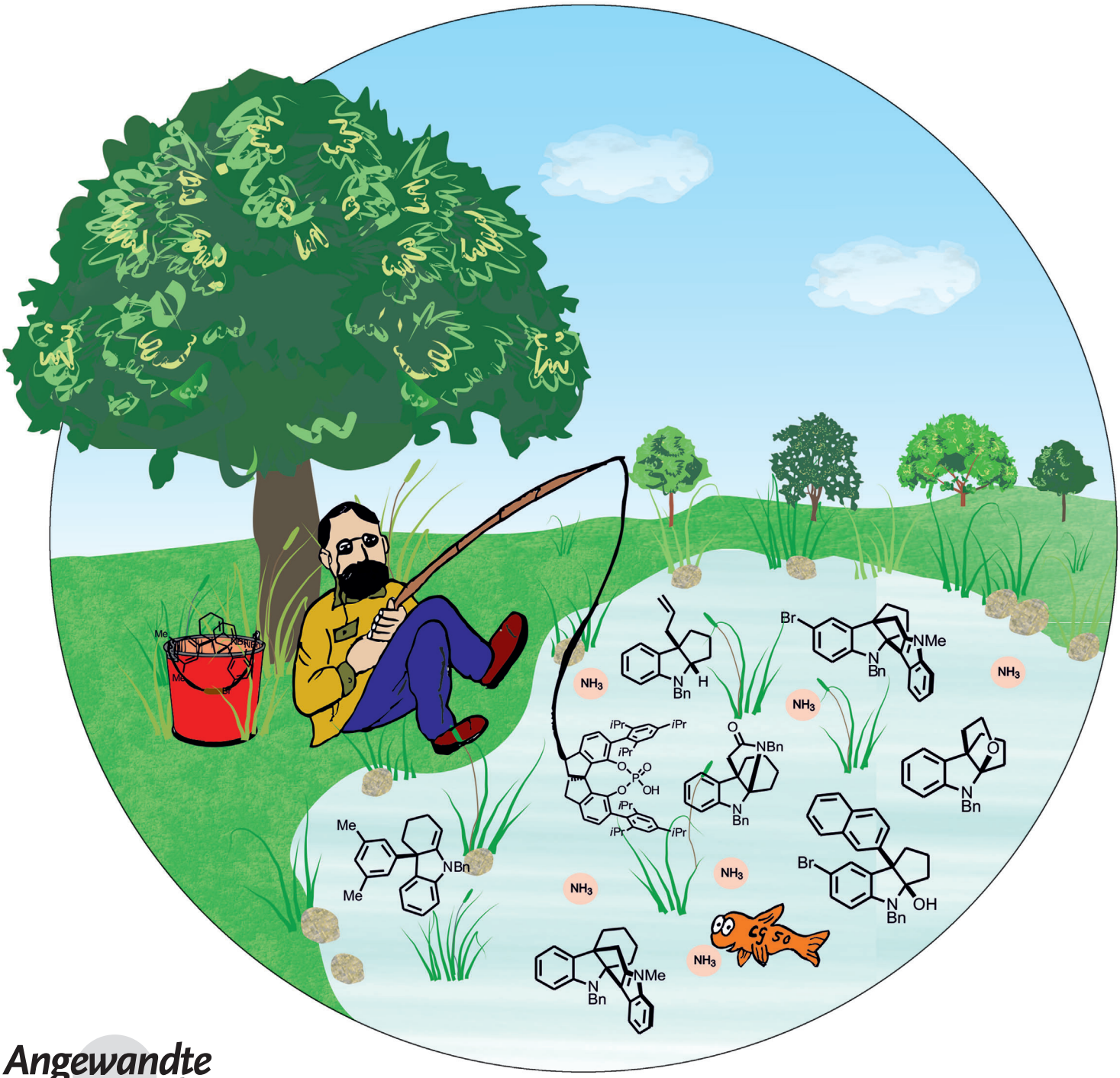
Brønsted Acid Catalysis

DOI: 10.1002/anie.201301618

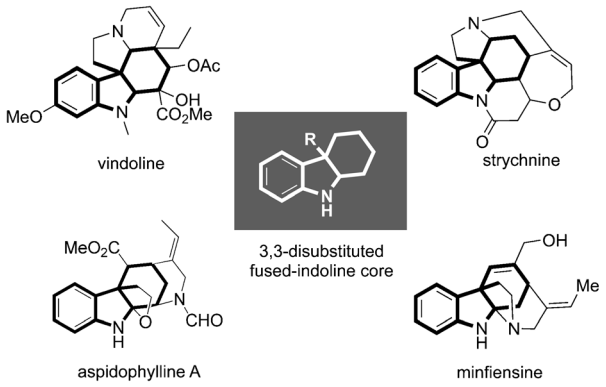
Versatile Access to Chiral Indolines by Catalytic Asymmetric Fischer Indolization**

*Alberto Martínez, Matthew J. Webber, Steffen Müller, and Benjamin List**

Dedicated to the Bayer company on the occasion of its 150th anniversary



3,3-Disubstituted fused indolines are privileged substructures of diverse natural products, and their synthesis has attracted intense attention (Scheme 1).[1,2] While a number of enantio-

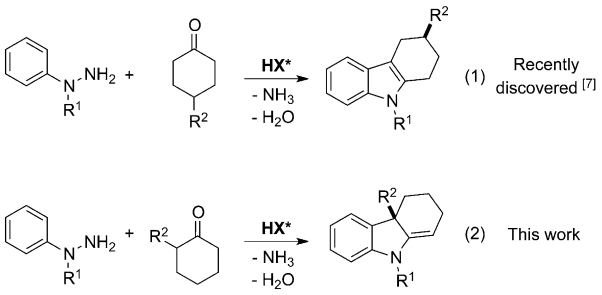


Scheme 1. Examples of natural products containing 3,3-disubstituted fused indoline cores.

selective approaches to monosubstituted indolines have been reported,[3] the asymmetric synthesis of challenging 3,3-disubstituted indoline targets has been less developed.[4] A recent achievement in this field of research has been the work of MacMillan et al., who employed a Diels–Alder-Michael addition cascade to enantioselectively generate precursors for a number of indole alkaloid total syntheses,[5] illustrating the potential of organocatalysis for natural product synthesis.[6] Herein we report a complementary strategy to 3,3-disubstituted fused-indolines based on the Fischer indolization, in which the formation of the indole scaffold itself serves as the basis for asymmetric induction.

Recently, our group developed an organocatalytic asymmetric variant of the Fischer indole synthesis [Scheme 2, Equation (1)].[7] We speculated that this procedure, originally designed for the synthesis of chiral 3-substituted tetrahydrocarbazoles, could potentially have further-reaching applications in organic synthesis, just as the non-asymmetric version has had throughout its long history.[8] For example, we envisaged that upon condensation of an α-substituted cyclic ketone with a phenylhydrazine, a chiral Brønsted acid catalyzed [3,3]-sigmatropic rearrangement of the higher substituted ene–hydrazine would lead to an enantioenriched fused indoline [Scheme 2, Equation (2)].[9,10]

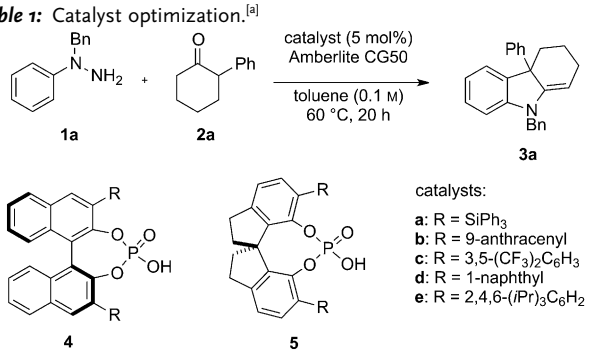
With this plan in mind, we began our studies with commercially available *N*-benzyl-*N*-phenylhydrazine (**1a**)



Scheme 2. Potential formation of enantioenriched 3,3-disubstituted fused indolines. HX* = chiral Brønsted acid.

and 2-phenylcyclohexanone (**2a**). In the presence of a range of chiral phosphoric acids and the weakly acidic cation exchange polymer Amberlite CG50, indoline–enamine **3a** could indeed be obtained in promising yields and enantioselectivities (Table 1).[11]

Table 1: Catalyst optimization.[a]



Entry	Catalyst	Yield [%][b]	e.r.[c]
1	**4a**	81	60:40
2	**4c**	84	68:32
3	**4d**	81	71.5:28.5
4	**4e**	82	59:41
5	**5b**	99	87:13
6	**5c**	97	64:36
7	**5e**	99	93.5:6.5
8[d]	**5e**	15	93.5:6.5

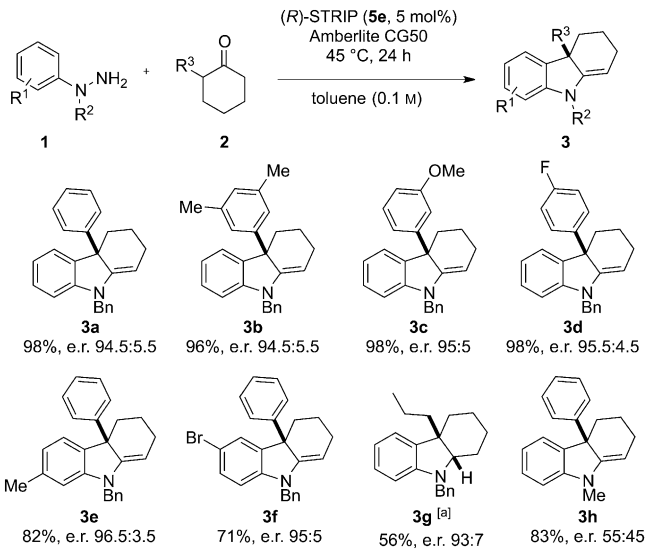
[a] Reactions were run on a 0.05 mmol scale with 50 mg of Amberlite CG50. Bn = benzyl. [b] Determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Amberlite CG50 omitted from the reaction mixture.

Both BINOL-[12] and SPINOL-derived[13] phosphoric acids were employed, and it was noticeable that the highest yields were obtained with SPINOL-derived catalysts (Table 1, entries 5–7). Moreover, the hindered SPINOL phosphoric acid STRIP (**5e**), previously introduced by our group,[13b] was seen to comfortably outperform its BINOL analogue TRIP (**4e**)[14] in terms of enantioselectivity (Table 1, entries 4 and 7). Thus (*R*)-STRIP became the catalyst of choice for further studies.[15] The importance of the weakly acidic CG50 polymer was then underlined by running the reaction in its absence (Table 1, entry 8). A poor yield (15%) was obtained, which is

[*] Dr. A. Martínez,[+] Dr. M. J. Webber,[+] Dr. S. Müller, Prof. Dr. B. List
Max-Planck-Institut für Kohlenforschung
Kaiser Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
E-mail: list@mpi-muelheim.mpg.de
[+] These authors contributed equally to this work.
[**] Generous support by the Max Planck Society is acknowledged. We also thank our HPLC and crystallography departments for their support.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301618.

thought to be due to the build-up of ammonia, inhibiting protonation of the key ene–hydrazine intermediate and drastically hindering turnover of the acid catalyst (e.r. 93.5:6.5 with or without polymer).[7]

We next turned our attention to assessing the substrate scope of the reaction (Scheme 3). It was found that indoline **3a** could be quantitatively furnished in 24 h at 45 °C and with

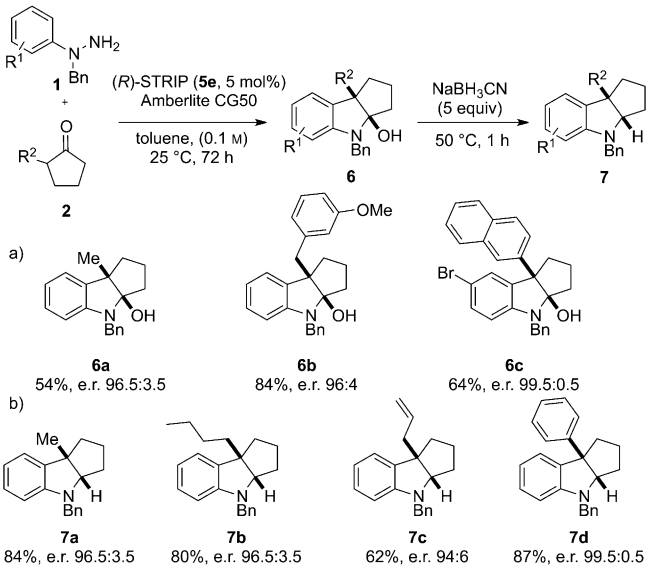


Scheme 3. Substrate scope for the synthesis of indoline derivatives. [a] After in situ reduction of the unstable enamine with $NaBH_3CN$.

an enantiomeric ratio (e.r.) of 94.5:5.5.[16] Varying the aryl substituent R^3 had little effect on either yield or e.r. (**3a**–**d**), while more marked effects were revealed when varying the starting hydrazine. First, the introduction of a methyl group in the 3-position of the hydrazine gave a single regioisomeric product **3e** with improved enantioselectivity compared to the unsubstituted analogue. A bromo substituent was well tolerated (**3f**, e.r. 95:5). 2-Alkylcyclohexanones proved to be less reactive (the reaction was carried out at 50 °C for 36 h). One example was the isolation of the *n*-propylindoline derivative **3g** in moderate yield as a mixture of diastereisomers (d.r. 8.5:1) after in situ reduction of the corresponding unstable enamine with $NaBH_3CN$. NOE-NMR studies showed that the major diastereoisomer was the *cis*-fused system with an e.r. of 93:7.

The presence of a benzyl group on the nitrogen atom was found to be essential for the enantioselectivity of the reaction. This is illustrated by the synthesis of product **3h** bearing an *N*-methyl group, with a poor e.r. of 55:45. It should be noted that all of the reactions were regioselective, with rearrangement taking place at the most substituted α-position of the starting ketone. The possible 1-substituted tetrahydrocarbazoles were not observed in any case.[9]

Encouraged by these results with cyclohexanones, we were compelled to pursue opportunities with 2-substituted cyclopentanone substrates (Scheme 4). Such substrates have previously been put forward as challenging for the Fischer indolization, with the products apparently showing instability to the usual rather harsh conditions of the reaction.[17] We

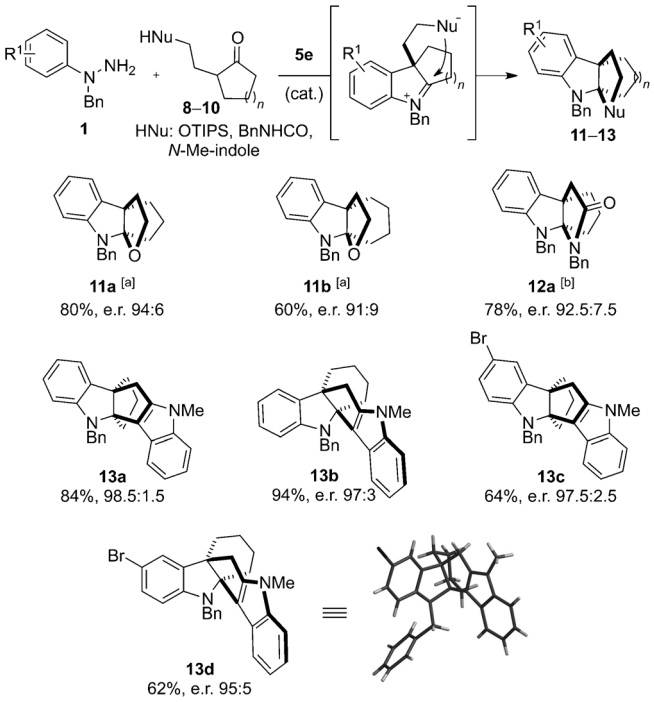


Scheme 4. Synthesis of a) 2-hydroxyindolines **6** and b) indolines **7** after in situ reduction with $NaBH_3CN$ post-indolization.

hoped that under our mild conditions, synthetically useful yields would be obtained. Interestingly, we were able to isolate 2-hydroxyindolines of type **6**, rather than the corresponding indoline–enamines. Alkyl and benzyl substituents were well-tolerated (**6a**,**b**), and incorporation of a naphthyl substituent led to indoline product **6c** with remarkably high enantioselectivity of 99.5:0.5.

The moderate yield obtained for methyl-substituted indoline **6a** (54%) is due to its instability to chromatographic purification methods. We supposed that the yield of the process could be improved by incorporating a reductive step to the reaction sequence. Indeed, adding $NaBH_3CN$ to the reaction mixture once indolization was judged to be complete resulted in an improved yield of 84% of reduced indoline **7a**. Methyl-substituted products **6a** and **7a** were obtained with identical e.r. of 96.5:3.5. In a similar fashion, reduced indoline products **7b**,**c** could also be obtained in good yields and high enantioselectivity. Once again, the presence of an aryl group in the substrate led to the indoline product with outstanding enantioselectivity (e.r. 99.5:0.5 for **7d** with $R^2 = Ph$).

After confirming that our catalytic system could successfully form enantioenriched 3,3-disubstituted fused indolines, we intended to apply this method for the synthesis of more complex molecules. We envisaged that by appropriate design of the starting ketone, the Fischer indolization pathway could be interrupted by the attack of an appropriate tethered nucleophile on the iminium functionality, which is formed upon the loss of ammonia (Scheme 5). This could give rapid access to polycyclic cores, which are present in a number of natural products. The so-called interrupted Fischer indolization has been widely studied, most recently by the group of Garg.[18,19] However, approaches to render the process asymmetric have so far been limited to a single example, employing an excess of a chiral phosphoric acid and inducing moderate enantioselectivity.[18b] We wished to harness the power of our Fischer indolization process to deliver a catalytic

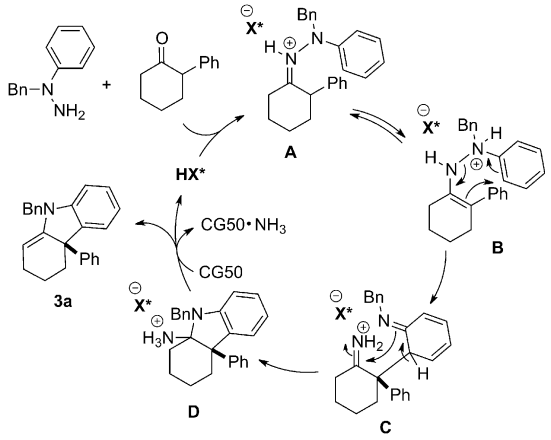


Scheme 5. Catalytic asymmetric interrupted Fischer indolization furnishing enantioenriched (hetero)propellanes. [a] TBAF addition; [b] 70 °C for 3 h after indolization. Nu = nucleophile, TIPS = triisopropylsilyl.

asymmetric variant of this complexity-generating reaction. With this idea in mind, we prepared a range of 5- and 6-membered cyclic ketones bearing oxygen, nitrogen, and carbon nucleophiles at the appropriate positions, which were then subjected to our optimized catalytic system in the presence of different phenyl hydrazines (Scheme 5).

Ketones containing a γ-silyl ether on the side chain reacted smoothly with hydrazine **1a** and, after in situ treatment with TBAF, the corresponding [3.3.3]- and [3.3.4]-oxapropellane furoindolines **11a**,**b** were obtained in good yields and enantioselectivities. Protection of the hydroxy group with a silyl group is crucial to achieve a high e.r.[20] In the case of amide-containing ketones, the temperature had to be increased upon completion of the indolization to accelerate the ring closure by nucleophilic attack of the amide nitrogen atom. Thus indoline **12a** was obtained in moderate yield and good enantioselectivity. Finally, to study ketones bearing a carbon nucleophile, we incorporated an electron-rich *N*-methylindole into its side chain. To the best of our knowledge, there had been no prior examples of an interrupted Fischer indolization featuring a carbon-based nucleophile. The investigated ketone substrates reacted efficiently with hydrazines **1a** and **1c** to give the polycyclic indolines **13a–d** bearing two vicinal quaternary stereocenters in good yields and enantioselectivities.[21] In both cases yields obtained for the hydrazine **1c**, bearing bromine in the aromatic ring, were lower owing to the slower reaction rate relative to the unsubstituted hydrazine **1a**. The absolute configuration of the indolo–indoline **13d** was unambiguously assigned by X-ray structural analysis (see the Supporting Information).

Scheme 6 shows the proposed catalytic cycle, which is in agreement with the accepted mechanism of the Fischer indolization.[22] We suggest that chiral phosphoric acid **5e** catalyzes the formation of protonated hydrazone **A**, followed



Scheme 6. Plausible catalytic cycle of formation of **3a**.

by tautomerization to the thermodynamically more stable cationic enehydrazine isomer **B**. The enantioselectivity-determining key step would then be the irreversible [3,3]-sigmatropic rearrangement of intermediate **B**, directed by the chiral phosphate counteranion, affording ion pair **C**. Upon ring closure, aminal **D** eliminates one equivalent of ammonia to give the final product **3a**. Ammonia is trapped by the cation-exchange polymer Amberlite CG50, allowing the turnover of the catalytic system.

In summary, we wish to emphasize the potential power of the catalytic asymmetric Fischer indole synthesis to rapidly access highly diverse indoline scaffolds, often displaying considerable structural complexity, in a single step from simple starting materials. The process has been developed to the extent that it may now offer an attractive approach towards the asymmetric synthesis of a wide variety of indole-containing targets under mild reaction conditions. Research along these lines is currently underway within our group.

Experimental Section

Representative procedure: A reaction vial was charged with (*R*)-STRIP (**5e**, 3.60 mg, 0.005 mmol), Amberlite CG50 (100 mg), 1-benzyl-1-phenylhydrazine (**1a**, 19.8 mg, 0.100 mmol), and 2-phenylcyclohexanone (**2a**, 17.4 mg, 0.100 mmol). Toluene (1.0 mL) was added and the resulting mixture was stirred in the sealed vial at 45 °C for 24 h. The crude reaction mixture was directly submitted to column chromatography on SiO_2, eluting with hexanes/EtOAc (97:3). Product **3a** was obtained as a colorless solid (32.9 mg, 98 %, e.r. 94.5:4.5).

Received: February 25, 2013
Published online: April 29, 2013

Keywords: Brønsted acid catalysis · Fischer indole synthesis · heterocycles · indoline · organocatalysis

[1] a) D. Zhang, H. Song, Y. Qin, *Acc. Chem. Res.* **2011**, *44*, 447 – 457; b) E. Attorusso, O. Taglialatela-Scafati, *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*, Wiley-VCH, Weinheim, **2008**; c) N. H. Greig, X.-F. Pei, T. T. Soncrant, D. K. Ingram, A. Brossi, *Med. Res. Rev.* **1995**, *15*, 3 – 31.

[2] Total synthesis of (−)-vindoline: a) D. Kato, Y. Sasaki, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 3685 – 3687; (−)-strychnine: b) S. D. Knight, L. E. Overman, G. Pairaudeau, *J. Am. Chem. Soc.* **1993**, *115*, 9293 – 9294; (±)-aspidophylline A: c) L. Zu, B. W. Boal, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 8877 – 8879; (+)-minfiensine: d) A. B. Dounay, L. E. Overman, A. D. Wrobleski, *J. Am. Chem. Soc.* **2005**, *127*, 10186 – 10187; e) S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606 – 13607; (±)-vincorine: f) M. Zhang, X. Huang, L. Shen, Y. Qin, *J. Am. Chem. Soc.* **2009**, *131*, 6013 – 6020.

[3] For selected examples, see: a) W. F. Bailey, M. J. Mealy, *J. Am. Chem. Soc.* **2000**, *122*, 6787 – 6788; b) G. S. Gil, U. M. Groth, *J. Am. Chem. Soc.* **2000**, *122*, 6789 – 6790; c) R. Kuwano, K. Kaneda, T. Ito, K. Sato, T. Kurokawa, Y. Ito, *Org. Lett.* **2004**, *6*, 2213 – 2215; d) R. Kuwano, M. Kashiwabara, *Org. Lett.* **2006**, *8*, 2653 – 2655; e) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8909 – 8911; f) D.-S. Wang, J. Tang, Y.-G. Zhou, M.-W. Chen, C.-B. Yu, Y. Duan, G.-F. Jiang, *Chem. Sci.* **2011**, *2*, 803 – 806; g) M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Angew. Chem.* **2011**, *123*, 7576 – 7579; *Angew. Chem. Int. Ed.* **2011**, *50*, 7438 – 7441; h) T. Saget, S. J. Lemouzy, N. Cramer, *Angew. Chem.* **2012**, *124*, 2281 – 2285; *Angew. Chem. Int. Ed.* **2012**, *51*, 2238 – 2242.

[4] For selected recent examples, see: a) B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314 – 6315; b) A. Pinto, Y. Jia, L. Neuville, J. Zhu, *Chem. Eur. J.* **2007**, *13*, 961 – 967; c) U. Groth, P. Köttgen, P. Langenbach, A. Lindenmaier, T. Schütz, M. Wiegand, *Synlett* **2008**, 1301 – 1304; d) J.-C. Hsieh, S. Ebata, Y. Nakao, T. Hiyama, *Synlett* **2010**, 1709 – 1711; e) Q. Cai, C. Zheng, J.-W. Zhang, S.-L. You, *Angew. Chem.* **2011**, *123*, 8824 – 8828; *Angew. Chem. Int. Ed.* **2011**, *50*, 8665 – 8669; f) Q.-F. Wu, C. Zheng, S.-L. You, *Angew. Chem.* **2012**, *124*, 1712 – 1715; *Angew. Chem. Int. Ed.* **2012**, *51*, 1680 – 1683; g) Z. Zhang, J. C. Antilla, *Angew. Chem.* **2012**, *124*, 11948 – 11952; *Angew. Chem. Int. Ed.* **2012**, *51*, 11778 – 11782; h) Q. Cai, S.-L. You, *Org. Lett.* **2012**, *14*, 3040 – 3043; i) Q. Cai, C. Liu, X.-W. Liang, S.-L. You, *Org. Lett.* **2012**, *14*, 4588 – 4590.

[5] S. B. Jones, B. Simmons, A. Mastacchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183 – 188.

[6] For examples of organocatalytic reactions towards natural product syntheses, see: a) R. Marcia de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575 – 2600; b) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167 – 178; c) M. Wasser, *Asymmetric Organocatalysis in Natural Product Syntheses*, Springer, Wien, **2012**; d) M. Christmann, *Science of Synthesis Asymmetric Organocatalysis 1*, *Lewis Base and Acid Catalysts*, Thieme, Stuttgart, **2012**, pp. 439 – 454.

[7] S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534 – 18537.

[8] For reviews on the applications of the Fischer indole synthesis, see: a) B. Robinson, *Chem. Rev.* **1963**, *63*, 373 – 401; b) B. Robinson, *Chem. Rev.* **1969**, *69*, 227 – 250; c) B. Robinson, *The Fischer Indole Synthesis*, Wiley-Interscience: New York, **1982**.

[9] For a study on the regioselectivity of Fischer indolizations of 2-substituted cyclohexanones, see: K. H. Pausacker, *J. Chem. Soc.* **1950**, 621 – 624.

[10] For reviews on asymmetric counteranion-directed catalysis, see: a) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603 – 614; b) M. Mahlau, B. List, *Isr. J. Chem.* **2012**, *52*, 630 – 638; c) J. Lacour, V. Hebbe-Viton, *Chem. Soc. Rev.* **2003**, *32*, 373 – 382; d) M. Mahlau, B. List, *Angew. Chem.* **2013**, *125*, 540 – 556; *Angew. Chem. Int. Ed.* **2013**, *52*, 518 – 533.

[11] For a rare previous example of a related racemic reaction, see: B. Cox, B. Robinson, *J. Heterocycl. Chem.* **1988**, *25*, 271 – 272.

[12] 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.

[13] 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.

[14] G. Adair, S. Mukherjee, B. List, *Aldrichimica Acta* **2008**, *41*, 31 – 39.

[15] Reaction conditions were screened in parallel with 2-butylcyclopentanone. See the Supporting Information for details.

[16] At the lower temperature of 25 °C, a higher e.r. could be obtained at the expense of slow conversion (74 %, e.r. 95.5:4.5, 5 days).

[17] a) N. P. Buu-Hoï, P. Jacquignon, T. B. Loc, *J. Chem. Soc.* **1958**, 738 – 740; b) A. H. Kelly, D. H. McLeod, J. Parrick, *Can. J. Chem.* **1965**, *43*, 296 – 301; c) J. Shimizu, S. Murakami, T. Oishi, Y. Ban, *Chem. Pharm. Bull.* **1971**, *19*, 2561 – 2566.

[18] For recent studies for the interrupted Fischer indolization using latent aldehydes in acid media, see: a) B. W. Boal, A. W. Schammel, N. K. Garg, *Org. Lett.* **2009**, *11*, 3458 – 3461; b) A. W. Schammel, B. W. Boal, L. Zu, T. Mesganaw, N. K. Garg, *Tetrahedron* **2010**, *66*, 4687 – 4695.

[19] For first examples of interrupted Fischer indolization reactions, see: a) S. Takano, M. Moriya, Y. Iwabuchi, K. Ogasawara, *Chem. Lett.* **1990**, 109 – 112; b) A. Z. Britten, W. G. Bardsley, C. M. Hill, *Tetrahedron* **1971**, *27*, 5631 – 5639; c) P. Rosenmund, E. Sadri, *Liebigs Ann. Chem.* **1979**, 927 – 943; d) P. Rosenmund, S. Gektidis, H. Brill, R. Kalbe, *Tetrahedron Lett.* **1989**, *30*, 61 – 62.

[20] 2-(2-hydroxyethyl)cyclopentanone gives low enantioselectivity under the optimal conditions (e.r. 62:38 at 25 °C).

[21] Low enantioselectivity was achieved using *N*-H-indole derivative as a starting material (e.r. 82:18 at 25 °C).

[22] For the original proposal of this mechanism, see: G. M. Robinson, R. Robinson, *J. Chem. Soc. Trans.* **1924**, *125*, 827 – 840.

