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Asymmetric Synthesis of Indolines by Catalytic Enantioselective Reduction of 3*H*-Indoles

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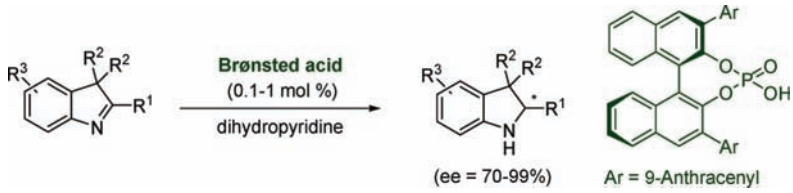
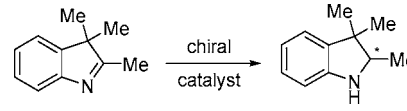
ABSTRACT



A highly enantioselective metal-free reduction of 3*H*-indoles has been developed. This Brønsted acid catalyzed transfer hydrogenation of indole derivatives with Hantzsch dihydropyridine as the hydrogen source constitutes an efficient method for the synthesis of various optically active indolines with high enantioselectivities.

Imine reduction continues to be a topic of ongoing interest with considerable efforts devoted to the asymmetric reduction of both cyclic and acyclic imines.[1] While many highly enantioselective hydrogenations of various imines and N-heteroaromatic compounds are known,[1] only a few asymmetric reductions of trisubstituted indoles are available. Current methods include transition metal catalyzed high-pressure hydrogenation using iridium and ruthenium complexes with a variety of chiral diphosphine,[2] diamine,[3] and phosphoramidite ligands.[4] However, all these methods are at present limited to 2,3,3-trimethylindole as the model substrate and yield the corresponding trimethylindoline in moderate to good enantioselectivities (Scheme 1).[2−4]

Scheme 1. Asymmetric Reduction of 2,3,3-Trimethylindole



Recently, chiral Brønsted acid catalysis[5,6] has become a major area in asymmetric synthesis, and several examples

(1) (a) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Syn. Catal.* **2003**, *345*, 103. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (c) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 2004; Suppl. 1, p 43. (d) Roszkowski, P.; Czarnocki, Z. *Mini-Rev. Org. Chem.* **2007**, *4*, 190. (e) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472. (f) Zhou, H.; Li, Z.; Wang, Z.; Wang, T.; Xu, L.; He, Y.; Fan, Q. H.; Pan, J.; Gu, L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 8464. (g) Wang, C.; Li, C.; Wu, X.; Pettman, A.; Xiao, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6524. (h) Wang, D. W.; Wang, X. B.; Wang, D. S.; Lu, S. M.; Zhou, Y. G.; Li, Y. X. *J. Org. Chem.* **2009**, *74*, 2780. (i) Spindler, F.; Blaser, H.-U. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; p 1193. (j) Claver, C.; Fernandez, E. In *Modern Reduction Methods*; Andersson, P. G., Munslow, I. J., Eds.; Wiley-VCH: Weinheim, 2008; p 237.

(2) (a) Chan, Y. N. C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400. (b) Morimoto, T.; Nakajima, N.; Achiwa, K. *Synlett* **1995**, 748. (c) Giernoth, R.; Krumm, M. S. *Adv. Synth. Catal.* **2004**, *346*, 989. (d) Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W. Y.; Li, Y. M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955. (e) Blaser, H. U.; Buser, H. P.; Häusel, R.; Jalett, H. P.; Spindler, F. *J. Organomet. Chem.* **2001**, *621*, 34. (f) Zhu, G.; Zhang, X. *Tetrahedron: Asymmetry* **1998**, *9*, 2415. (g) Liu, D.; Li, W.; Zhang, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2181.

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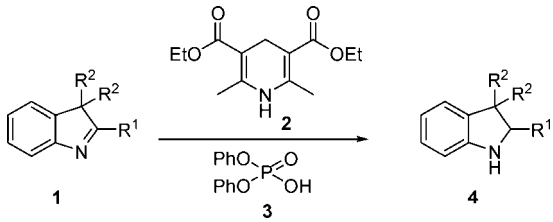
of highly enantioselective metal-free hydrogenation of carbon−nitrogen double bonds based on chiral phosphoric acid catalysts have been reported.[7−9]

In the present communication, we describe the first general enantioselective Brønsted acid catalyzed hydrogenation of 3*H*-indoles. Inspired by the success of chiral Brønsted acids in the reduction of imines,[8a] quinolines,[8b,e] benzoxazines,[8c] and pyridines,[8d] we decided to evaluate them in the first organocatalytic reduction of 3*H*-indoles. In an initial phase, various achiral proton acids were tested. It was found that diphenyl phosphates **3** readily catalyze the reduction of 3*H*-indoles **1** with Hantzsch dihydropyridine **2** as a hydrogen source (Scheme 2).[10]

Scheme 2. Metal-Free Reduction of Trisubstituted Indoles



This prompted us to explore the enantioselective version of this process to develop the first Brønsted acid catalyzed reduction of 3*H*-indoles. For this purpose, chiral Brønsted acids **5a**−**j** were applied in the reduction of 3*H*-indole **1a** (Table 1).[11]

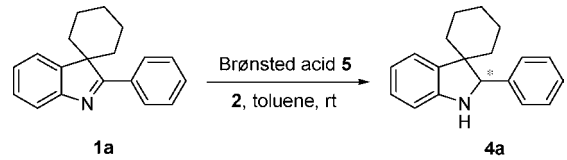
Initially, the asymmetric transfer hydrogenation was performed in toluene with imine **1a** as the test substrate, Hantzsch dihydropyridine **2** as the hydrogen source, and Brønsted acids **5a**−**j** as catalysts. From these experiments, Brønsted acid **5j** emerged as the most suitable catalyst for this transformation, yielding the product **4a** in an excellent yield and selectivity (98%, 97% ee).

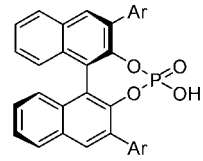
Further experiments concentrated on the optimization of other reaction parameters such as temperature, concentration, and catalyst loading. While lowering the temperature resulted in inferior conversion, decreasing the concentration yielded diminished enantioselectivity.

Using a more concentrated solution resulted in a drop in both conversion and enantioselectivity, indicating that product inhibition occurs. The influence of the catalyst loading on the reduction of 3*H*-indole **1a** to indoline **4a**, is summarized in Table 2. Decreasing the catalyst loading to 1 mol % had no influence on the conversion and selectivity (Table 2, entry 2). Furthermore, despite a lower conversion, the catalyst loading could be decreased to 0.1 mol % without affecting the selectivity (Table 2, entry 3).

Under the optimized conditions, the scope of the Brønsted acid catalyzed hydrogenation of various *3H*-indoles was explored (Tables 3 and 4). In general, high yields and

Table 1. Survey of Chiral Catalysts for the Hydrogenation



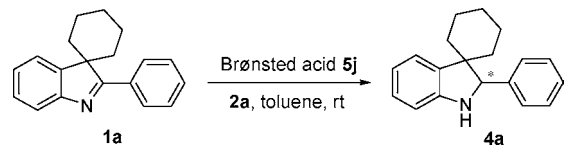


5a: Ar = 9-Phenanthryl
5b: Ar = $[H]_8Ph_3Si$
5c: Ar = Phenyl
5d: Ar = 4-Biphenyl
5e: Ar = 1-Naphthyl
5f: Ar = 2-Naphthyl
5g: Ar = 3,5-$(CF_3)C_6H_3$
5h: Ar = 3,5-$(t\text{-}Bu)_2$PMP
5i: Ar = $[H]_8$-9-Phenanthryl
5j: Ar = 9-Anthracenyl

entry[a]	catalyst	yield [%][b]	ee [%][c]
1	**5a**	96	72
2	**5b**	94	50
3	**5c**	98	42
4	**5d**	96	38
5	**5e**	75	48
6	**5f**	89	42
7	**5g**	96	10
8	**5h**	82	4
9	**5i**	91	72
10	**5j**	98	97

[a] Reactions were performed at rt with 3*H*-indole **1a**, **2** (1.25 equiv), and 5 mol % catalyst **5** at 0.02 M concentration in toluene for 16 h. [b] Yield after column chromatography. [c] Enantiomeric excess was determined by HPLC on a chiral phase.

Table 2. Examination of the Catalyst Loading



entry[a]	**5j** [mol %]	yield [%][b]	ee [%][c]
1	**5**	99	97
2	**1**	97	97
3	**0.1**	81	96

[a] Reactions were performed at rt with 3*H*-indole **1a**, **2** (1.25 equiv), and catalyst **5** at 0.02 M concentration in toluene for 16 h. [b] Yield after column chromatography. [c] Enantiomeric excess was determined by HPLC on a chiral phase.

(3) (a) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195. (b) Fuentes, J. A.; Clarke, M. L.; Slawin, A. M. Z. *New J. Chem.* **2008**, *32*, 689.

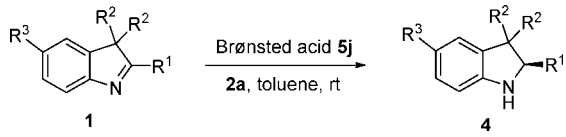
(4) Faller, J. W.; Milheiro, S. C.; Parr, J. *J. Organomet. Chem.* **2006**, *691*, 4945.

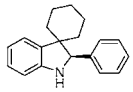
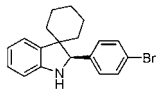
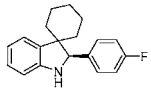
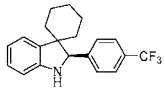
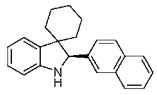
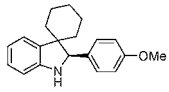
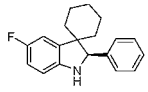
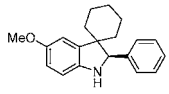
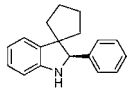
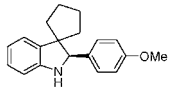
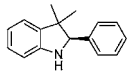
(5) For reviews on chiral Brønsted acid catalysis, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520; *Angew. Chem.* **2006**, *118*, 1550. (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (f) Yamamoto, H.; Payette, N. In *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH: Weinheim, 2009; p 73.

(6) For reviews on chiral phosphoric acids catalysts, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Terada, M. *Chem. Commun.* **2008**, 4097. (c) Terada, M. *Synthesis* **2010**, 1929.

(7) For a recent overview, see: Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2010**, 852.

Table 3. Scope of the Catalytic Enantioselective Reduction

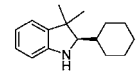
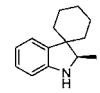
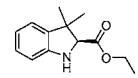


entry[a]	indoline **4**	yield [%][b]	ee [%][c]
1		99	97
2		88	>99
3		91	>99
4		93	>99
5		86	99
6		84	>99
7		93	98
8		92	97
9		91	97
10		94	97
11		92	96

[a] Reactions were performed at rt with 3*H*-indole **1**, **2** (1.25 equiv), and 1 mol % catalyst **5** at 0.02 M concentration in toluene for 16 h. [b] Yield after column chromatography. [c] Enantiomeric excess was determined by HPLC on a chiral phase.

excellent enantioselectivities were obtained in the case of 2-aryl-substituted *3H*-indoles (Table 2, entries 1−11). The reaction tolerates various electron-donating and electron-withdrawing substituents on both the aryl substituent and indoline core. However, only moderate to high yields and selectivities were obtained if 2-alkyl-substituted indoles were reduced (Table 4, entries 1−4).

Table 4. Scope of the Catalytic Enantioselective Reduction

entry[a]	indoline **4**	yield [%][b]	ee [%][c]
1		54	76[d]
2		86	75[e]
3		71	70[e]
4		87	90[f]

[a] Reactions were performed with 3*H*-indole **1**, **2** (1.25 equiv), and 1 mol % catalyst **5** at 0.02 M concentration in toluene for 16 h. [b] Yield after column chromatography. [c] Enantiomeric excess was determined by HPLC on a chiral phase. [d] 2 days, 50 °C, 32% starting material isolated. [e] Catalyst **5b**, 3 days, 50 °C. [f] 5 mol % **5j**, rt.

Employing CD spectroscopy measurements and theoretical calculations, the absolute configuration of 2-phenyl 3,3-dimethyl indoline (Table 3, entry 11) has been determined as (*S*).[12] The stereochemical outcome of the reaction is in agreement with our previous results obtained in the asymmetric reduction of 2-substituted N-heterocyles.

In summary, we developed the first metal-free enantioselective Brønsted acid catalyzed transfer hydrogenation of 3*H*-

(8) Selected reductions from our group: (a) Rueping, M.; Azap, C.; Sugiono, E.; Theissmann, T. *Synlett* **2005**, 2367. (b) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (c) Rueping, M.; Theissmann, T.; Antonchick, A. P. *Synlett* **2006**, 1071. (d) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (e) Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 1001. (f) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562. (g) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751. (h) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 5836. (i) Kadyrov, R.; Koenigs, R. M.; Brinkmann, C.; Voigtlaender, D.; Rueping, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7556. (j) Rueping, M.; Tato, F.; Schoepke, F. R. *Chem.—Eur. J.* **2010**, *16*, 2688. (k) Rueping, M.; Stoeckel, M.; Sugiono, E.; Theissmann, T. *Tetrahedron* **2010**, *66*, 6565. (l) Rueping, M.; Sugiono, E.; Steck, A.; Theissmann, T. *Adv. Synth. Catal.* **2010**, *352*, 281. (m) Rueping, M.; Theissmann, T. *Chem. Sci.* **2010**, *1*, 473. (n) Rueping, M.; Koenigs, R. M. *Chem. Commun.* **2010**, in print.

(9) Selected chiral phosphoric acid catalyzed C=N reductions from other groups: (a) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (b) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (d) Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180. (e) Kang, Q.; Zhao, Z. A.; You, S. L. *Adv. Synth. Catal.* **2007**, *349*, 1657. (f) Li, G. L.; Liang, Y. X.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830. (g) Kang, Q.; Zhao, Z. A.; You, S. L. *Org. Lett.* **2008**, *10*, 2031. (h) Guo, Q. S.; Du, D. M.; Xu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 759. (i) Han, Z.-Y.; Xiao, H.; Gong, L.-Z. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3729.

(10) For recent reviews on HEH reductions: (a) Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327. (b) You, S. L. *Chem. Asian J.* **2007**, *2*, 820. (c) Connon, S. J. *Org. Biomol. Chem.* **2007**, *5*, 3407. (d) Wang, C.; Wu, X. F.; Xiao, J. L. *Chem. Asian J.* **2008**, *3*, 1750. (e) For a study on the hydride-donor abilities of HEH see: (f) Richter, D.; Mayr, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1958.

(11) The free Brønsted acids **5a**−**j** are the actual catalysts.

(12) For details see Supporting Information.

indoles. The mild reaction conditions, low catalyst loading, and high enantioselectivities render this transformation an attractive approach to optically active indolines.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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