CHEMISTRY
A EUROPEAN JOURNAL

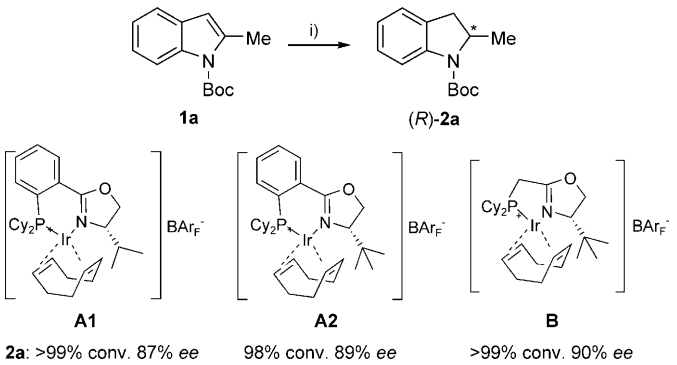
DOI: 10.1002/chem.200903105

Iridium-Catalyzed Asymmetric Hydrogenation of N-Protected Indoles

Alejandro Baeza and Andreas Pfaltz*[a]

Chiral indolines are common structures occurring in alkaloids and other natural or synthetic products that exhibit biological activity.[1] In addition, indolines with a stereogenic center at C-2 have been used as organocatalysts or chiral auxiliaries in asymmetric transformations.[2] Different methods have been developed to obtain such molecules in an enantioselective manner; however, only a few catalytic methods have been reported, most of them based on enzymatic or nonenzymatic kinetic resolutions.[3] One of the best methods in terms of simplicity and atom efficiency would be the direct asymmetric hydrogenation of substituted indoles, but this reaction, along with the hydrogenation of other heteroaromatic compounds, still represents a challenge.[4] The only suitable catalysts for this transformation reported so far are based on the *trans*-coordinating diphosphine (*S,S*)-(*R,R*)-PhTRAP ligand paired with rhodium or ruthenium.[5] Hydrogenation with these catalysts in the presence of base allowed the preparation of 2- or 3-substituted indolines in high enantiomeric purity. Herein we report another efficient class of catalysts for the asymmetric hydrogenation of N-protected indoles, cationic Ir complexes derived from PHOX or other chiral N,P ligands.[6]

Initial studies were carried out on unprotected 2-methyl and 2-phenyl indoles, but only moderate conversions and enantioselectivities were obtained. Methylation of the nitrogen atom improved the conversion but, disappointingly, the enantioselectivity dropped sharply.[7] In contrast to the findings of Kuwano and Ito,[5] addition of base or other additives led to worse results. We next turned to *N*-Boc-protected indoles, using the 2-methyl derivative **1a** as test substrate. After an exhaustive screening of catalysts, we found that iridium complexes bearing an electron-rich dialkyl-phosphane group provided the best results.[7] Thus, Ir-PHOX complexes **A1** and **A2**, along with catalyst **B**[8] and the pyridine-based catalyst **C**[9] were identified as optimal catalysts for this reaction, giving the best conversions and enantioselectivities. After refinement of the reaction parameters, such as hydrogen pressure, catalyst loading, and solvent,[7] full conversion and high enantioselectivities were achieved within 6 h at ambient temperature and 50 bar of hydrogen pressure in dichloromethane when using catalysts **A1**, **A2**, or **B** (Scheme 1).



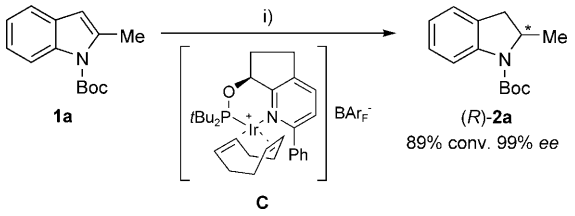
Scheme 1. Asymmetric hydrogenation of indole **1a** with catalysts **A1**, **A2** and **B**. i) H_2 (50 bar), cat. (1 mol%), CH_2Cl_2, 25 °C, 6 h.

With catalyst **C**, which had already proved to be effective in the asymmetric hydrogenation of furans and benzofurans,[9] perfect enantioselectivity was obtained (>99% *ee*), although the conversion remained moderate. Increase of catalyst loading, temperature and reaction time gave only minor improvements.[7] Kinetic measurements showed that the reaction came to a halt after 8 h; this implies that catalyst deactivation was the problem. Consequently, the catalyst was added in two portions, 2 mol% in the beginning and 2 mol% after 8 h. In this way, 89% conversion was achieved at 60 °C and 100 bar hydrogen pressure, while the enantiomeric excess remained at 99% despite the elevated reaction temperature (Scheme 2).

Next the influence of different substituents at C-5 of the indole nucleus was examined (Table 1). The presence of

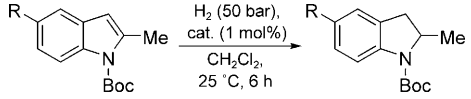
[a] Dr. A. Baeza, Prof. A. Pfaltz
Department of Chemistry, University of Basel
St. Johanns Ring 19, 4056 Basel (Switzerland)
Fax: (+41) 61-267-1103
E-mail: andreas.pfaltz@unibas.ch

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903105 and contains details and analytical data for the compounds.



Scheme 2. Asymmetric hydrogenation of indole **1a** using catalysts **C**. i) H_2 (100 bar), **C** (4 mol%), CH_2Cl_2, 60°C, 24 h.

Table 1. Effect of substituents in the asymmetric hydrogenation of indoles **1**.

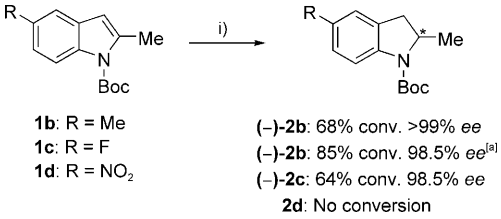


	1b		1c	
Catalyst	Conv. [%][a]	*ee* [%][b]	Conv. [%][a]	ee [%][b]
A1	87	90	58	84
A2	81	95	43	88
B	>99	95	98	84

[a] Determind by ^{1}H NMR analysis after removal of the catalyst (see the Supporting Information for details). [b] Determind by HPLC analysis on a Daicel Chiralcel OD-H column (see the Supporting Information for details).

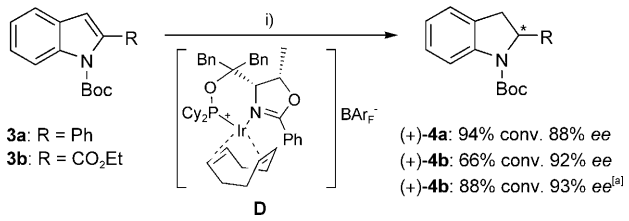
either an electron-donating group, like methoxy (**1b**), or an electron-withdrawing substituent, like fluorine (**1c**), led to a decrease in the conversion. The methoxy group had a positive effect on the enantioselectivity, whereas the fluoro derivative gave somewhat lower *ee* values than the unsubstituted indole **1a** (Table 1). Catalyst **B** turned out to be especially active as compared to PHOX complexes **A1** and **A2**, and excellent conversions were obtained even with these substrates. The 5-nitro derivative **1d**, on the other hand, did not react under these conditions.

The same trend for the hydrogenation of indoles **1b** and **1c** was observed with catalyst **C**.[7] Since conversions were even lower than with the standard substrate **1a**, the sequential catalyst addition strategy was again adopted, leading to moderate conversions and excellent enantioselectivities (Scheme 3). In chlorobenzene at 110°C, the enantioselectivity was still very high, while the conversion increased to 85%.[10]



Scheme 3. Effect of substituents in the asymmetric hydrogenation of indoles **1**. i) H_2 (100 bar), **C** (4 mol%), CH_2Cl_2, 60°C, 24 h. [a] With PhCl as solvent and at 110°C.

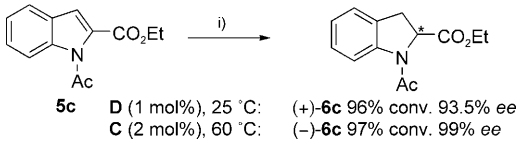
Other substituents at the 2 position were also examined. Thus, 2-phenyl and 2-carboethoxy-substituted *N*-Boc-protected indoles **2a** and **2b** were subjected to hydrogenation using the catalysts and conditions mentioned above. However, the results were disappointing, especially with substrate **3b**, which gave the corresponding deprotected indole as the main product in most cases. To our delight, the Ir-ThrePHOX complex **D**[11] proved to be much more effective in this case. The 2-phenyl derivative gave 94% conversion and 88% *ee* with this catalyst under the conditions shown in Scheme 4. In the hydrogenation of substrate **3b**, partial



Scheme 4. Asymmetric Hydrogenation of 2-subsituted *N*-Boc indoles **3a** and **3b**. i) H_2 (75 bar), **D** (1 mol%), CH_2Cl_2, 25°C, 24 h. [a] At 100 bar H_2 pressure and with 2 mol% catalyst loading.

cleavage of the Boc group was observed. However, this problem was overcome by simply increasing the catalyst loading (up to 2 mol%) and the hydrogen pressure (100 bar). Finally, 3-substituted indoles were also tested but, disappointingly, gave only low or no conversion.

In addition to Boc, other common nitrogen protecting groups were evaluated. *N*-Acetyl-2-phenylindole reacted with high enantioselectivity, similar to the *N*-Boc-protected analogue, but conversions were low.[7] In contrast, high conversions and excellent enantioselectivities were achieved with the 2-carboethoxy derivative **5c** (Scheme 5). Among

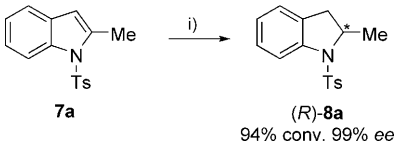


Scheme 5. Asymmetric hydrogenation of 2-subsituted *N*-Ac indole **5c**. i) H_2 (100 bar), cat., CH_2Cl_2, 30 h.

the catalysts tested, the pyridine-based complex **C** gave the highest enantiomeric excess (99% *ee*). However, more vigorous conditions than for the more reactive catalyst **D** had to be applied to achieve high conversion. *N*-Acetyl-3-carbomethoxyindole, on the other hand, did not react with these catalysts, even under forcing conditions. *N*-Acetyl-3-methylindole also proved to be very unreactive. Although *ee* values of up to 93% were achieved, conversions remained low (<35%).

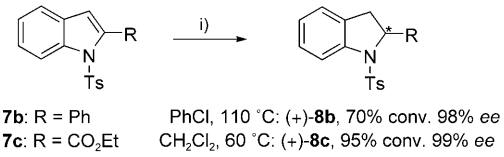
Finally we turned our attention to *N*-tosyl-protected indoles. The 2-methylindole **7a** was found to be less reactive than the *N*-Boc derivative, requiring long reaction times and

high H_2 pressure, but the enantioselectivities were considerably higher (99% *ee* for catalysts **A2** and **B**).[7] As observed for the *N*-Boc derivative, complex **B** proved to be the most reactive catalyst, giving high conversion under the conditions shown in Scheme 6. The need for more forcing conditions could be due to coordination of the catalyst to the sulfone group, which could lower the activity of the catalyst, but on the other hand cause the remarkable increase in enantioselectivity (Scheme 6).



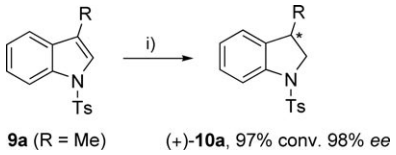
Scheme 6. Asymmetric hydrogenation of 2-subsituted *N*-tosyl indole **7a**. i) H_2 (100 bar), **B** (2 mol%), CH_2Cl_2, 25°C, 30 h.

Next, other 2-substituted *N*-tosyl-indoles were examined. As before, 2-phenyl and 2-carboethoxyindole **7b** and **7c** were subjected to hydrogenation under the conditions used for **7a**. The best results were obtained with catalyst **C** but, despite high enantioselectivities, the conversions remained low. However, with higher catalyst loading and sequential catalyst addition (see above), we were able to successfully hydrogenate substrate **7c** with high conversion and excellent enantioselectivity when the temperature was raised to 60°C (Scheme 7). However, when the same conditions were applied to the 2-phenylindole **7b**, conversion only reached 55%. Even at 110°C in chlorobenzene the conversion did not exceed 70%. On the other hand, the enantiomeric excess remained at 98% despite the high temperature (Scheme 7).



Scheme 7. Asymmetric hydrogenation of 2-subsituted *N*-tosyl indoles **7b** and **7c**. i) H_2 (100 bar), **C** (4 mol%), solvent, 24 h.

Among the 3-substituted *N*-tosylindoles, the 3-methyl derivative **9a** reacted with perfect enantioselectivity (>99% *ee*) when using catalyst **C** under standard conditions, but the conversion was moderate (52%). Therefore, the reaction was carried out at elevated temperature (Scheme 8). Most gratifyingly, almost quantitative conversion was achieved at 60°C, while the *ee* remained at very high level of 98%. *N*-Tosylindoles with carboxylic ester groups at C-3 (**9b**, R = CO_2Me; **9c**, R = CH_2CO_2Et) showed extremely low reactivity and gave only very low or no conversion at all, even under forcing conditions.



Scheme 8. Asymmetric hydrogenation of 3-subsituted *N*-tosyl indoles **9a**. i) H_2 (100 bar), **C** (2.5 mol%), CH_2Cl_2, 60°C, 30 h.

In summary, our results show that cationic Ir catalysts with chiral N,P ligands are efficient catalysts for the asymmetric hydrogenation of N-protected indoles. The *ee* values are in the same range as those reported for Ru and Rh complexes with the (*S,S*)-(*R,R*)-PhTRAP ligand, which were the only suitable catalysts known for this substrate class up to now.[5] However, in contrast to Rh- and Ru-catalyzed hydrogenations, no base additives are needed. A further advantage of the Ir catalysts is their air and moisture stability. The results obtained with *N*-Boc-, *N*-acetyl-, and *N*-tosylindoles demonstrate that the protecting group influences both the reactivity and enantiomeric excess. With the right combination of catalyst and protecting group, high yields and excellent enantioselectivities can be achieved for various 2- and 3-substituted indoles.

Experimental Section

General procedure for the iridium-catalyzed asymmetric hydrogenation of N-protected indoles: A solution of the N-protected indole (0.2 mmol) and the iridium complex (1–2.5 mol%) in dry dichloromethane (1 mL, previously filtered over basic alumina) under an inert atmosphere was placed in an autoclave, which was sealed, purged with hydrogen, and pressurized to the desired hydrogen pressure. After the mixture had been stirred at the desired temperature for the indicated time, the solvent was evaporated, and the catalyst was removed by filtration through a short silica gel column (3×1 cm) with pentane/diethyl ether (1:1, 25 mL) as eluent to give the corresponding N-protected indoline after evaporation of the solvent.

When the reaction was carried out with sequential addition of catalyst, the same procedure was followed, but after 8 h at the reported temperature, the autoclave was allowed to cool down to 30–40°C and opened after the hydrogen pressure had been released. Then a solution of the iridium complex in the corresponding dry solvent (100 μL, previously filtered over basic alumina) was syringed into the reaction vessel. The autoclave was sealed again, purged with hydrogen, and repressurized. Then stirring was continued at the reported temperature for an additional 16 h.

For catalyst screening, reactions were performed on a 0.1 mmol scale.

A preparative experiment was also carried out by using 2-methyl-*N*-Boc-protected indole **1a** and catalyst **A2**. The general procedure was followed, but using a 0.4 M solution (instead of 0.2 M) of **1a** (578 mg, 2.5 mmol) in chlorobenzene (6.25 mL) and 1 mol% of **A2** catalyst (38 mg). After the mixture had been stirred at 25°C under H_2 (50 bar) for 6 h. The solvent was evaporated, and the catalyst was removed by filtration through a silica gel column (2×12 cm) with pentane/diethyl ether (1:1, 100 mL) as eluent. The pure indoline **2a** was obtained in 94% yield (544 mg) with 92% *ee*.

Acknowledgements

A.B. would like to thank the Spanish Ministerio de Educación, Ciencia y Deporte (MECD) and Fundación Española para la Ciencia y la Tecnología (FECYT) for a Postdoctoral fellowship. Support of this work by the Swiss National Science Foundation and the Federal Commission for Technology and Innovation (KTI) is gratefully acknowledged.

Keywords: asymmetric catalysis · hydrogenation · indoles · indolines · iridium

[1] For example, see: a) I. W. Southon, J. Buckingham in *Dictionary of Alkaloids*, Chapman and Hall, New York, **1989**; b) N. Neuss, M. N. Neuss in *The Alkaloids* (Eds.: A. Brossi, M. Suffness), Academic Press, San Diego, **1990**, p. 229; c) F. Gueritte, J. Fahy in *Anticancer Agents from Natural Products* (Eds.: G. M. Cragg, D. G. I. Kingstom, D. J. Newman), CRC Press, Boca Raton, **2005**, p. 123; d) *Modern Alkaloids* (Eds.: E. Fattorusso, O. Taglialatela-Scafati), Wiley-VCH, Weinheim, **2008**, and references therein.

[2] Selected examples: a) R. K. Kunz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3240–3241; b) F. Andersson, E. Hedenström, *Tetrahedron: Asymmetry* **2006**, *17*, 1952–1957; c) A. Hartikka, P. I. Arvidsson, *J. Org. Chem.* **2007**, *72*, 5874–5877, and references therein.

[3] Selected examples: a) B. Orsat, P. B. Alper, W. Moree, C.-P. Mak, C.-H. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 712–713; b) V. Gotor-Fernández, P. Fernández-Torres, V. Gotor, *Tetrahedron: Asymmetry* **2006**, *17*, 2558–2564; c) F. O. Arp, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 14264–14265; d) X. L. Hou, B. H. Zheng, *Org. Lett.* **2009**, *11*, 1789–1791; e) S. Anas, H. B. Kagan, *Tetrahedron: Asymmetry* **2009**, *20*, 2193–2199, and references therein.

[4] Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357–1366, and references therein.

[5] a) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614–7615; b) R. Kuwano, K. Kaneda, T. Ito, K. Sato, T. Kurokawa, Y. Ito, *Org. Lett.* **2004**, *6*, 2213–2215; c) R. Kuwano, M. Kashiwabara, *Org. Lett.* **2006**, *8*, 2653–2655; d) R. Kuwano, M. Kashiwabara, K. Sato, T. Ito, K. Kaneda, Y. Ito, *Tetrahedron: Asymmetry* **2006**, *17*, 521–535. The same catalytic system has recently been applied to the asymmetric hydrogenation of *N*-Boc-substituted pyrroles: e) R. Kuwano, M. Kashiwabara, M. Ohsumi, H. Kusano, *J. Am. Chem. Soc.* **2008**, *130*, 808–809.

[6] Reviews: a) S. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402–1411; b) K. Källström, I. Munslow, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 3194–3200; c) X. Cui, K. Burgess, *Chem. Rev.* **2005**, *105*, 3272–3296.

[7] See the Supporting Information for details.

[8] For the use of these catalysts for the asymmetric hydrogenation of tetrasubstituted olefins, see: M. G. Schrems, E. Neumann, A. Pfaltz, *Angew. Chem.* **2007**, *119*, 8422–8424; *Angew. Chem. Int. Ed.* **2007**, *46*, 8274–8276.

[9] a) S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem.* **2006**, *118*, 5318–5321; *Angew. Chem. Int. Ed.* **2006**, *45*, 5194–5197. For other application of these catalysts, see: b) S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642–644; c) A. Wang, B. Wüstenberg, A. Pfaltz, *Angew. Chem.* **2008**, *120*, 2330–2332; *Angew. Chem. Int. Ed.* **2008**, *47*, 2298–2300; d) A. Baeza, A. Pfaltz, *Chem. Eur. J.* **2009**, *15*, 2266–2269.

[10] When these conditions were applied to substrate **1c**, partial deprotection was observed. The lower *ee* of the deprotected product indicates that cleavage of the *N*-Boc group occurs (at least in part) before hydrogenation, because unprotected indoles were found to react with lower enantioselectivity than N-protected derivatives.

[11] a) F. Menges, A. Pfaltz, *Adv. Synth. Catal.* **2002**, *344*, 40–44; b) S. McIntyre, E. Hörmann, F. Menges, S. P. Smidt, A. Pfaltz, *Adv. Synth. Catal.* **2005**, *347*, 282–288; c) A. Baeza, A. Pfaltz, *Synlett* **2008**, 3167–3171.

Received: November 12, 2009
Published online: January 26, 2010

