Catalytic Asymmetric Hydrogenation of Heteroaromatic Compounds, Indoles

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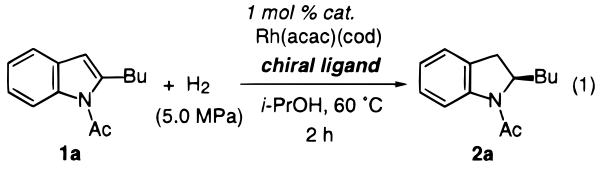
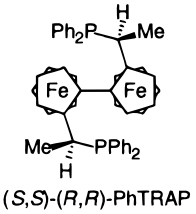
Catalytic asymmetric hydrogenations of prochiral unsaturated compounds,[1] olefin,[2] ketone,[3] and imine,[4] have been intensively studied and are considered as a versatile method of creating a chiral carbon center.[5] However, no highly enantioselective hydrogenation of heteroaromatic groups has so far been reported except that of 2-methylquinoxaline to our knowledge.[6] Resonance stability of heteroaromatic compounds might impede the enantioselective hydrogenation,[7] which may find potentially wide applicability in stereoselective organic synthesis.[8,9] Herein, we describe the highly enantioselective hydrogenation of heteroaromatic compounds, indoles.

We recently disclosed that the rhodium complex generated from Rh(acac)(cod) and PPh_3 is a good catalyst for the hydrogenation of five-membered heteroaromatic compounds.[10] Thus chiral rhodium complexes prepared in situ from Rh(acac)(cod) and various commercially available chiral bisphosphines (1 mol %) were examined for asymmetric hydrogenation of *N*-acetyl-2-butylindole (**1a**) at 60 °C for 2 h with 5.0 MPa of H_2 in 2-propanol (eq 1), resulting in non-enantioselective hydrogenation (0−1% ee).[11] Fortunately, the successful asymmetric hydrogenation has been achieved by use of a trans-chelating chiral bisphosphine ligand, (*S*,*S*)-(*R*,*R*)-PhTRAP,[12,13] giving (*R*)-*N*-acetyl-2-butylindoline (**2a**) with 85% ee (77% conversion). No reduction of the fused aromatic ring of **1a** was observed.





On further investigation into the asymmetric hydrogenation, $[Rh(nbd)_2]SbF_6$ was found to be superior to Rh(acac)(cod) as catalyst precursor (Table 1). It is noted that addition of base is necessary for achievement of high enantioselectivity as well as high catalytic activity. The $[Rh(nbd)_2]SbF_6$−(*S*,*S*)-(*R*,*R*)-PhTRAP catalyst scarcely promoted the hydrogenation in the absence of base, giving a trace of **2a** with only 7% ee (*S*) (entry 1). Addition of 10 mol % of Et_3N or Cs_2CO_3 brought remarkable improvement of the enantioselectivity and catalytic activity (100% conversion, 94% ee (*R*)) (entries 2 and 3).[14] Both the enantioselectivity and catalytic activity were significantly dependent upon base: K_2CO_3 gave (*R*)-**2a** with 76% ee, and pyridine did not activate the cationic PhTRAP−rhodium complex at all (entries 4 and 5). The amount of Cs_2CO_3 did not affect the selectivity: 20 mol %, 94% ee; 1 mol %, 93% ee. It is possible to carry out the asymmetric hydrogenation at lower pressure (1.0 MPa) without significant decrease of the selectivity and reaction rate (entry 6). The amount of PhTRAP−rhodium complex can be reduced to 0.1 mol %, and the reaction was completed within 20 h to give (*R*)-**2a** of 93% ee in 92% isolated yield (entry 7).

Table 1. Catalytic Asymmetric Hydrogenation of **1a**[a]

entry	base	$P(H_2)$, MPa	temp °C	convn,[b] %	ee,[c] %
1	none	5.0	60	trace	7 (*S*)
2	Et_3N	5.0	60	100	94 (*R*)
3	Cs_2CO_3	5.0	60	100	94 (*R*)
4	K_2CO_3	5.0	60	44	76 (*R*)
5	pyridine	5.0	60	0	
6	Cs_2CO_3	1.0	60	100	92 (*R*)
7[d]	Cs_2CO_3	10.0	60	100[e]	93 (*R*)

[a] Reactions were carried out in 2-propanol (2.0 mL) for 2 h. **1a** (0.5 mmol)/$[Rh(nbd)_2]SbF_6$/(*S*,*S*)-(*R*,*R*)-PhTRAP/base was 100/1.0/1.05/10 unless otherwise noted. [b] Determined by ^1H NMR analysis of crude product. [c] Determined by HPLC analysis with CHIRALPAK AD. [d] **1a**/$[Rh(nbd)_2]SbF_6$/(*S*,*S*)-(*R*,*R*)-PhTRAP/Cs_2CO_3 was 1000/1.0/1.1/10. The reaction was carried out for 20 h. [e] 92% isolated yield.

Although 2-propanol has frequently been used as a hydrogen source in the transfer hydrogenation of unsaturated compounds

(1) For reviews, see: (a) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1994; pp 1−39. (b) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; pp 16−94.

(2) For reviews, see: (a) Pfaltz, A. In *Stereoselective Synthesis*; Helmchen, G., Hofmann, R. W., Mulzer, J., Schaumann, E., Eds.; Theime: Stuttgart, 1996; Vol. 7, pp 4334−4359. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 121−182. (c) Halterman, R. L. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 183−195.

(3) For reviews, see: (a) Brunner, H. In *Stereoselective Synthesis*; Helmchen, G., Hofmann, R. W., Mulzer, J., Schaumann, E., Eds.; Theime: Stuttgart, 1996; Vol. 7, pp 3945−3966. (b) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 199−246.

(4) For reviews, see: (a) Martens, J. In *Stereoselective Synthesis*; Helmchen, G., Hofmann, R. W., Mulzer, J., Schaumann, E., Eds.; Theime: Stuttgart, 1996; Vol. 7, pp 4199−4219. (b) Blaser, H.-U.; Springer, F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 247−265.

(5) For examples, see: (a) Schreiber, S. L.; Kelly, S. E.; Porco, J. A., Jr.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210−6218. (b) Kitamura, M.; Nagai, K.; Hsiao, Y.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 549−542. (c) Taber, D. F.; Wang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 22−26.

(6) Bianchini, C.; Barbaro, P.; Scapacci, G.; Farnetti, E.; Graziani, M. *Organometallics* **1998**, *17*, 3308−3310.

(7) For resonance energy of heteroaromatic compounds, see: Bird, C. W. *Tetrahedron Lett.* **1992**, *48*, 335−340.

(8) For reviews of the hydrogenation of heteroaromatic compounds, see: (a) Keay, J. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 579−602. (b) Gribble, G. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 603−633. (c) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031−15070.

(9) For examples, see: (a) Rossen, K.; Weissman, S. A.; Sager, J.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 6419−6422. (b) Gilchrist, T. L.; Graham, K.; Coulton, S. *Tetrahedron Lett.* **1995**, *36*, 8693−8696.

(10) Kuwano, R.; Sato, K.; Ito, Y. *Chem. Lett.* **2000**, 428−429.

(11) Representative results of using commercially available chiral bisphosphines were as follows: (*R*)-BINAP, 1% ee (*S*); (*R*)-(*S*)-BPPFA, 0% ee; (2*S*,3*S*)-Chiraphos, 1% ee (*S*); (−)-(2*R*, 3*R*)-DIOP, 0% ee; (2*S*, 4*S*)-BPPM, 0% ee; (*R*,*R*)-Me-DuPHOS, 0% ee.

(12) (*S*,*S*)-(*R*,*R*)-PhTRAP = (*R*,*R*)-2,2″-bis[(*S*)-(diphenylphosphino)ethyl]-1,1″-biferrocene.

(13) (a) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 593−596. (b) Sawamura, M.; Hamashima, H.; Sugawara, M.; Kuwano, R.; Ito, Y. *Organometallics* **1995**, *14*, 4549−4558.

(14) We presume that a Rh(I)H complex is an active species for the asymmetric hydrogenation (see ref 10). The base additive possibly deprotonates from a cationic $Rh(III)H_2$ complex, generating a neutral Rh(I)H complex. See: Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2134−2143.

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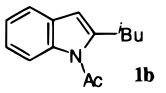
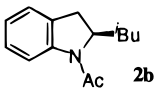
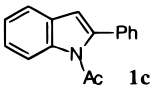
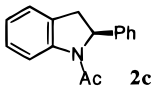
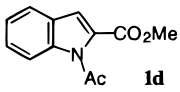
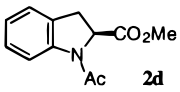
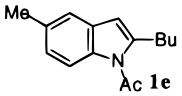
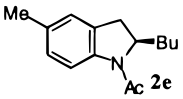
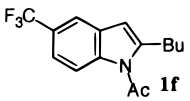
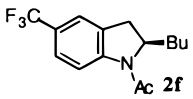
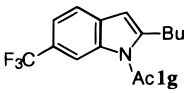
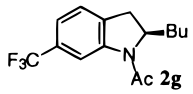
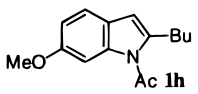
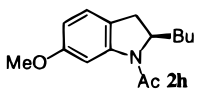
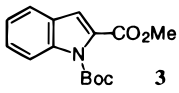
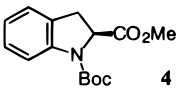
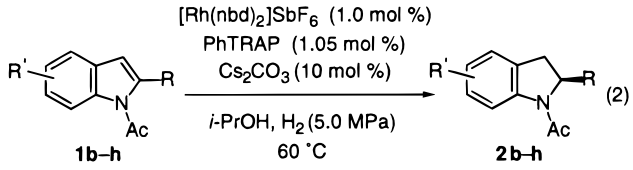
Table 2. Catalytic Asymmetric Hydrogenations of 2-Substituted Indoles[a]

entry	substrate	time h	product	yield[b] %	ee[c] %
1	 **1b**	2	 **2b**	91	91[d]
2	 **1c**	1	 **2c**	91	87
3[e]	 **1d**	0.5	 **2d**	95	95[f]
4	 **1e**	2	 **2e**	94	94
5	 **1f**	2	 **2f**	84	92
6	 **1g**	2	 **2g**	83	92
7	 **1h**	2	 **2h**	98	94
8	 **3**	2	 **4**	86	78[d]

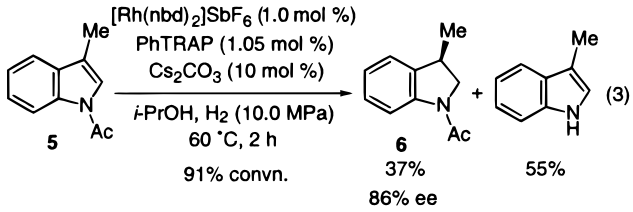
[a] Reactions were carried out at 60 °C and 5.0 MPa of H_2 in 2-propanol (2.0 mL) unless otherwise noted. **1** or **3** (0.5 mmol)/$[Rh(nbd)_2]SbF_6$/(*S*,*S*)-(*R*,*R*)-PhTRAP/Cs_2CO_3 was 100/1.0/1.05/10. [b] Isolated yield. [c] Determined by HPLC analysis with CHIRALPAK AD unless otherwise noted. [d] Determined by HPLC analysis with CHIRALCEL OD-H. [e] The reaction was carried out at 100 °C and 10.0 MPa. Et_3N was used instead of Cs_2CO_3. [f] Determined by HPLC analysis with CHIRALPAK AS.

using a transition metal complex,[15] such a possibility is ruled out by the experiment using H_2 and Rh(acac)(cod)-PhTRAP catalyst in 2-propanol-d_8. No product resulting from D_2 addition was detected in GC-MS analysis.[16,17]

A variety of 2-substituted indoles were hydrogenated into the corresponding indolines with high enantiomeric excesses in high yields (eq 2, Table 2). The hydrogenations of 2-isobutyl- and 2-phenylindole, **1b** and **1c**, proceeded with 91% ee and 87% ee, respectively (entries 1 and 2). With indole-2-carboxylate **1d**, the PhTRAP−rhodium complex failed in high asymmetric induction (79% ee) under the above conditions (60 °C, 5.0 MPa of H_2). Higher temperature and hydrogen pressure (100 °C, 10.0 MPa of H_2) were, however, favorable to the highly enantioselective



hydrogenation of **1d** (83% ee). Use of Et_3N instead of Cs_2CO_3 improved the enantioselectivity remarkably, providing (*S*)-**2d** with 95% ee (entry 3). The enantiomeric excess of **2** was little affected by the steric and electronic properties of the substituent on the fused aromatic ring of **1** (entries 4−7). The protective group on the nitrogen atom may play an important role in the enantioselection. *N*-Boc derivative **3** was converted into (*S*)-**4** with lower enantiomeric excess (entry 8).[18] Optically active 3-substituted indoline **6** could be obtained by use of the $[Rh(nbd)_2]SbF_6$−PhTRAP−Cs_2CO_3 catalyst, but the hydrogenation competed with the undesirable alcoholysis of **5** significantly (eq 3).



In summary, the catalytic asymmetric hydrogenation of indoles has been accomplished by use of the $[Rh(nbd)_2]SbF_6$−PhTRAP−base catalyst, providing a variety of optically active indolines with up to 95% ee. This is the first example of highly enantioselective hydrogenation of five-membered heteroaromatic compounds using asymmetric catalysis. Future work will be directed toward the development of highly enantioselective hydrogenation of other heteroaromatic compounds, pyrrole, furan, pyridine, etc.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) Spogliarich, R.; Tencich, A.; Kaspar, J.; Graziani, M. *J. Organomet. Chem.* **1982**, *240*, 453−459. (b) Saburi, M.; Ohnuki, M.; Ogasawara, M.; Takahashi, T.; Uchida, Y. *Tetrahedron Lett.* **1992**, *33*, 5783−5786. (c) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285−288. (d) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580−9588.

(16) The hydrogenation in 2-propanol-d_8 using the $[Rh(nbd)_2]SbF_6$−PhTRAP−Cs_2CO_3 catalyst also gave the product resulting from H_2 addition (confirmed by ^1H NMR analysis). However, the exchange of hydrogen for deuterium on the *N*-acetyl group was observed in this case.

(17) The reactions in other solvents also proceeded with high enantioselectivity and good catalyst activity: 92% conversion, 91% ee in toluene; 53% conversion, 87% ee in 1,2-dichloroethane; 52% conversion, 84% ee in THF.

(18) The hydrogenation of **3** proceeded with 46% ee (*S*) under the best conditions for the reduction of **1d** ($[Rh(nbd)_2]SbF_6$−PhTRAP−Et_3N catalyst, 100 °C, 10.0 MPa, 0.5 h).