Tetrahedron: *Asymmetry* 21 (2010) 2010–2014

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselective hydrogenation of indoles derivatives catalyzed by Walphos/rhodium complexes

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ARTICLE INFO

Article history:
Received 12 May 2010
Accepted 22 June 2010
Available online 24 July 2010

ABSTRACT

The enantioselective hydrogenation of indole esters has been carried out efficiently in the presence of a rhodium catalyst modified by Walphos-type chiral ligands. The addition of a base can be beneficial in some catalytic conditions.

1. Introduction

The enantioselective hydrogenation of heteroaromatic compounds constitutes a very powerful method to access chiral cyclic skeletons with a high potential for asymmetric synthesis.[1,2] However, the hydrogenation of heteroatomic derivatives has been less investigated than that of other classes of substrates such as enamides, β-keto esters, imines, and other olefins.[3] If quinoline, quinoxaline, and pyridine compounds have been reduced with excellent selectivities,[1,2] the five-membered heteroaromatic compounds, such as indole derivatives, have only been hydrogenated efficiently recently[4] in the presence of another catalytic system than that containing the *trans*-chelating bisphosphines of the Ph-TRAP family.[5] The Ph-TRAP-based catalytic systems suffer from a non-straightforward access to the chiral ligands.[6] Thus, the efficient hydrogenation of indole derivatives still remains a challenge with regard to the application of easily accessible chiral auxiliaries.[4]

Enantiomerically pure amino acids and their derivatives are well known as versatile building blocks for pharmaceutical applications and the efforts devoted to prepare non-proteinogenic amino acids remain relevant.[7] In order to carry out the hydrogenation of indole derivatives, the nitrogen atom needs to be derivatized in order to lower the aromaticity of the heterocycle. Thus, we focused on the preparation of enantiomerically enriched indoline carboxylic acid and specifically targeted the hydrogenation of *N*-Boc-indole esters. Generally, the Boc residue can be easily attached to an indole derivative and, subsequently, very easy to cleave.[8] Herein, we report on the enantioselective hydrogenation of *N*-Boc-2-substituted indole derivatives in the presence of rhodium catalysts generated from easily accessible bisphosphine ligands.

2. Results and discussion

For our initial experiments, we selected the 1-*tert*-butyl 2-methyl 1*H*-indole-1,2-dicarboxylate **1** as the model substrate. We first examined the cationic precursor $[Rh(nbd)_2]SbF_6$ in association with four selected commercially available chiral bisphosphines (Fig. 1).

The reactions were carried out according to Ito's[5a] reported conditions in *i*PrOH, at 60 °C, under 50 bar of hydrogen, and in the presence of a base (Scheme 1). The addition of a base has been found to be essential for the reaction to proceed.[5a] The results are reported in Table 1. All reactions were complete under our conditions. However, in addition to the expected indoline product **2**, we also observed the transesterified substrate **3**, two N-deprotected derivatives **4** and **5**, and the hydrogenated product **6** bearing an *iso*propyl ester (Scheme 1).

Compounds **4** and **5** result from the alcoholysis of **1** and **3**, respectively. The major products were the desired hydrogenated species **2** and the transesterified hydrogenated derivative **6**. For a test experiment, substrate **1** was heated at 60 °C for 2 h in propan-2-ol in the presence of 10 equiv of Cs_2CO_3. We observed up to 78% overall transesterification (**3**, 14% and **5**, 64%). Without a base, substrate **1** remained unchanged during heating in dry propan-2-ol for 2 h. The transesterification process could be entirely suppressed just by adding a few drops of water into the medium containing the base.[9] The base Cs_2CO_3 was thus identified as participating in both unwanted side reactions, that is, transesterification and alcoholysis. We were unable to determine the enantiomeric purity of **2** and **6** in the reaction mixtures as the HPLC signals overlapped. The next series of experiments were carried out under the aforementioned conditions, but in methanol instead of propan-2-ol. The results are given in Table 2. The crude reaction mixtures were composed of the hydrogenated product **2**, the

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doi:10.1016/j.tetasy.2010.06.030

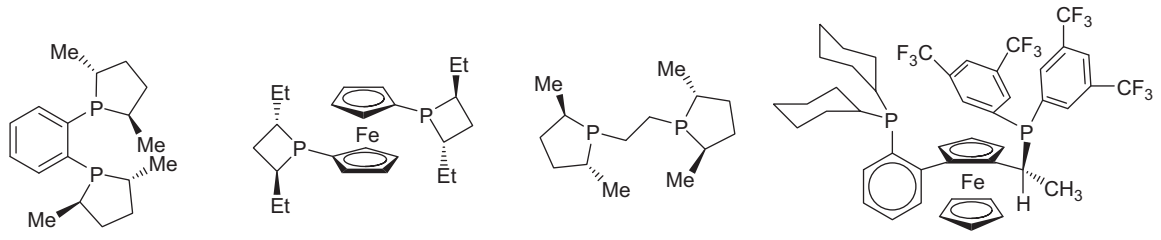
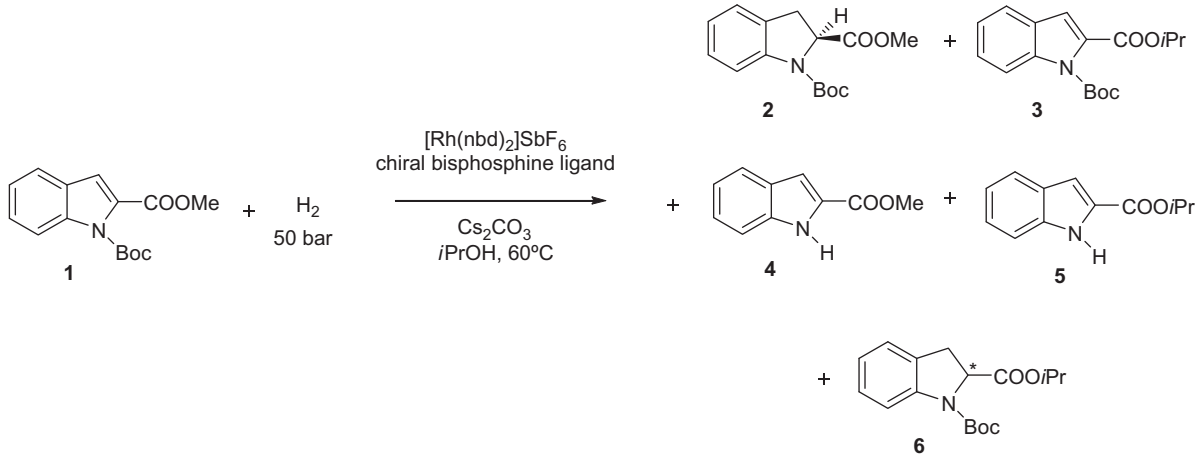


Figure 1. Chiral bisphosphine ligands applied in the asymmetric hydrogenation of 1-*tert*-butyl-2-methyl 1*H*-indole-1,2-dicarboxylate **1**.



Scheme 1. Asymmetric hydrogenation of 1-*tert*-butyl-2-methyl 1*H*-indole-1,2-dicarboxylate **1**.

Table 1
Enantioselective hydrogenation of 1-*tert*-butyl-2-methyl 1*H*-indole-1,2-dicarboxylate **1**[a]

Entry	Chiral auxiliary	Time (h)	Conv.[b] (%)	**2**[b] (%)	**3**[b] (%)	**4**[b] (%)	**5**[b] (%)	**6**[b] (%)
1	SL-W008-1	18	100	32	2	0.5	1.4	55
2	(*R*,*R*)-MeDUPHOS	90	99	13	2	0.3	6.4	65
3	EtFerroTANE	18	100	39	1.2	0	2.2	49
4	(*R*,*R*)-MeBPE	70	100	0.5	2	2.6	51	37

[a] **1**/[Rh(nbd)$_2$]SbF$_6$/ligand/Cs_2CO_3: 100/1/1/10; P_{H2} = 50 bar, 60 °C; 17 h, reaction time not optimized.
[b] Yield determined by GC.

Table 2
Evaluation of chiral ligands in the asymmetric hydrogenation of **1** in MeOH[a]

Entry	Chiral auxiliary	Time (h)	Conv.[b] (%)	**2**[b] (%)	**4**[b] (%)	ee of **2** (%)[c] (conf.)
1	SL-W008-1	2	100	71	26	38 (*R*)
2	(*R*,*R*)-MeDUPHOS	2	80	13	61	3 (*R*)
3	EtFerroTANE	17	100	45	54	44 (*R*)
4	(*R*,*R*)-MeBPE	17	100	8.6	91	20 (*R*)

[a] **1**/[Rh(nbd)$_2$]SbF$_6$/ligand/Cs_2CO_3: 100/1/1/10; P_{H2} = 50 bar, 60 °C; 17 h, reaction time not optimized.
[b] Determined by GC analysis.
[c] Determined by HPLC analysis.

N-deprotected derivative **4** and some unreacted substrate **1**. The alcoholysis side reaction became significantly more important in methanol (26–91%) than in propan-2-ol (0.3–2.6%, Table 1). In the presence of the Walphos ligand SL-W008-1 and EtFerroTANE, product **2** was obtained in 71% and 45% yield and 38% and 44% ee, accompanied by compound **4** in 26% and 54% yield, respectively (Table 2, entries 1 and 3). The chiral ligands MeDUPHOS and MeBPE induced lower yields of **2** (13% and 8.6%) and lower selectivities (3% and 20% ee, respectively) (Table 2, entries 2 and 4).

As the Walphos ligand SL-W008-1 furnished the best compromise between enantioselectivity and magnitude of alcoholysis and because of the large variety of congeners easily available,[10] we studied other ligands of that family. We also varied the source of rhodium precursors. We found that the neutral rhodium dimer [Rh(OH)(COD)]$_2$ provided more efficient catalysts than the cationic [Rh(nbd)$_2$]SbF$_6$. Finally, we altered the hydrogen pressure and the temperature and found that running the hydrogenations at room temperature under 100 bar of dihydrogen and in the presence of Cs_2CO_3 was the most appropriate conditions. The selected Walphos ligands are presented in Figure 2 and the hydrogenation results are summarized in Table 3.

Based on the observations detailed above and in order to limit the transesterification process, we applied three solvent/base systems: MeOH/Cs_2CO_3 (Table 3, entries 1–5); propan-2-ol without base (Table 3, entries 6–10); and propan-2-ol/H_2O/Cs_2CO_3 (Table 3, entries 11–15). The Walphos ligand SL-W008-1 combined with [Rh(OH)(COD)]$_2$ in MeOH in the presence of Cs_2CO_3 provided the most enantioselective catalytic system as **2** was obtained in 87% yield and 77% ee (Table 3, entry 4). The alcoholysis process occurred only in 1.6%. Ligand SL-W002-1 provided the highest yield of **2** (>98% conversion, >96.5% selectivity) (Table 3, entries 1, 6, and 11). The lowest level of alcoholysis was generally observed in the presence of this ligand as well (<0.4%). The chiral ligand inducing both the highest chemoselectivity and enantioselectivity of **2** was SL-W006-1 (100% conversion, 98% yield in **2**, 72% ee, no alcoholysis detected) (Table 3, entry 8). In this case, the reaction was carried out in dry propan-2-ol without the base. In a propan-2-ol/H_2O/Cs_2CO_3 solvent system, the enantioselectivity

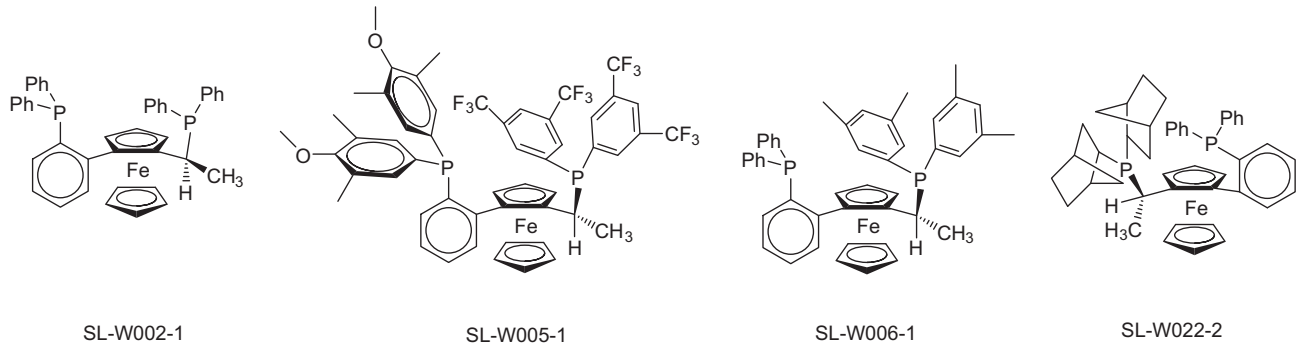


Figure 2. The Walphos ligands used in asymmetric hydrogenation of 1-*tert*-butyl-2-methyl 1*H*-indole-1,2-dicarboxylate **1**.

Table 3
Evaluation of Walphos-type ligands in the asymmetric hydrogenation of **1**[a]

Entry	Chiral auxiliary	Solvent	Cs_2CO_3 (equiv)	Conv.[b] (%)	**2**[b] (%)	**4**[b] (%)	ee of **2** (%)[c] (config.)
1	SL-W002-1	MeOH	50	99	99	0	66 (*R*)
2	SL-W005-1	MeOH	50	100	97	0.2	37 (*R*)
3	SL-W006-1	MeOH	50	94	90	1.5	27 (*S*)
4	SL-W008-1	MeOH	50	89	87	1.6	77 (*R*)
5	SL-W022-2	MeOH	50	69	66.5	1.5	34 (*R*)
6	SL-W002-1	*i*PrOH	—	100	97	0	66 (*R*)
7	SL-W005-1	*i*PrOH	—	100	95.5	0.1	0
8	SL-W006-1	*i*PrOH	—	100	98	0	72 (*S*)
9	SL-W008-1	*i*PrOH	—	97	86.5	1.1	9 (*R*)
10	SL-W022-2	*i*PrOH	—	89	83.5	1.6	34 (*R*)
11	SL-W002-1	*i*PrOH/H_2O	50	99	96.5	0.4	46 (*R*)
12	SL-W005-1	*i*PrOH/H_2O	50	99	99	0.4	35 (*R*)
13	SL-W006-1	*i*PrOH/H_2O	50	100	99	0.1	51 (*S*)
14	SL-W008-1	*i*PrOH/H_2O	50	65	63	2	16 (*R*)
15	SL-W022-2	*i*PrOH/H_2O	50	85	83	0.5	71 (*R*)

[a] **1**/[Rh(OH)(COD)]$_2$/ligand/Cs_2CO_3: 80/1/1/50; P_{H2} = 100 bar, room temperature; 17 h, reaction time not optimized.
[b] Determined by GC analysis.
[c] Determined by HPLC analysis.

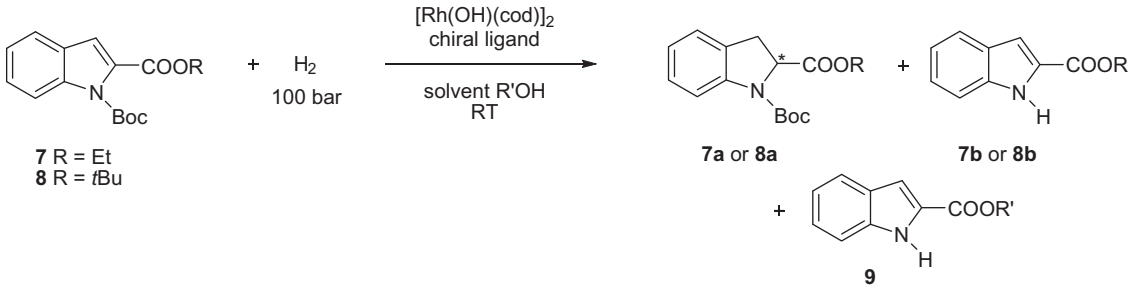
dropped significantly (51% ee, Table 3, entry 13). The most selective system in propan-2-ol/H_2O/Cs_2CO_3 was obtained with SL W022-2 (71% ee, Table 3, entry 15). It can be proposed that the alcoholysis process remains minor as long as the hydrogenation proceeds at a sufficiently high rate. The ability of the rhodium catalysts bearing Walphos-type ligands to perform efficient hydrogenations at room temperature is the key point as the alcoholysis is most probably inhibited at that temperature. For the asymmetric hydrogenation of the *N*-Boc indole derivative **1**, the catalytic system developed here compares well with the Rh/Ph-TRAP catalysts developed by Kuwano and Ito (78% ee).[5a]

Next, we applied our catalytic systems to other indole esters especially the ethyl **7** and *tert*-butyl **8** derivatives (Scheme 2) in order to improve the catalytic performance by increasing the steric demand of the substrate. To the best of our knowledge, the hydrogenation of **7** and **8** had not been carried out. We attempted a large variety of experimental conditions including different catalytic precursors, solvents, the presence of a base, and ferrocenyl ligands. The best results are summarized in Table 4.

In all cases, in addition to the hydrogenation product **7a** or **8a**, we also observed the deprotected derivatives **7b** or **8b** and eventually the transesterified, non-hydrogenated, and deprotected product **9**. Under our experimental conditions, for the two substrates, [Rh(OH)COD]$_2$ complex appeared to be the most suitable precatalyst at once in terms of activity and enantioselectivity. The first experiments with substrate **7** were performed in ethanol in order to avoid the transesterification (Table 4, entries 1 and 3) but conversions remained low (<37%) although the enantioselectivity was interesting (85%) with the SL-W008-1 ligand (Table 4, entry 1). Other combinations of solvents and ligands did not allow us to improve this result (Table 4, entries 2 and 4). Again, the most enantioselective catalytic system for the ethyl substrate is the same as that used for the methyl derivative. Next, we turned our attention to the *tert*-butyl ester **8**. As *tert*-butanol was prohibited as the solvent, we performed hydrogenations in 2-methylbutan-2-ol. The major product was the deprotected substrate **8b** (entry 5). We consequently decided to use MeOH or *i*PrOH. In addition to the hydrogenated product **8a** and the deprotected substrate **8b**, a small amount of deprotected transesterified derivative **9** was obtained (in the presence of water, entries 6 and 7, without the base, entry 8, Table 4). The various experiments including variation of the chiral ligand and the catalytic conditions (with or without water and with or without the base) shaved the catalytic system SL-W002-/**8**/[Rh(OH)COD]$_2$ in MeOH (Table 4, entry 8) to be the most effective catalytic system. An 85% yield of **8a** with an ee of 80% could be reached under these conditions, which provided the best result for an easy to implement hydrogenation of *N*-Boc-indole derivatives.

3. Conclusion

In conclusion, we have developed a new efficient catalytic system based on rhodium and chiral ligands of the Walphos family for the enantioselective hydrogenation of indole derivatives. These easily accessible catalytic systems are prepared in situ from commercially available diphosphines and readily accessible rhodium precursors. These new catalytic systems are efficient at room temperature in the presence of water. Small variations of the catalytic conditions allow optimizing of the system according to the properties desired



Scheme 2. Asymmetric hydrogenation of the 2-substituted indole esters **7** and **8**.

Table 4
Evaluation of ferrocenyl ligands in asymmetric hydrogenation of **7** and **8**[a]

Entry	Substrate	Chiral auxiliary	Solvent	Cs_2CO_3 (equiv/Rh)	Conv.[b] (%)	**7a** or **8a**[b] (%)	**7b** or **8b**[b] (%)	**9**[b] (%)	ee of **7a** or **8a** (%)[c] (config.)
1	**7**	SL-W008-1	EtOH	50	37	26	6	—	85 (*R*)
2	**7**		*i*PrOH/H_2O	50	80	28	49	—	71 (*R*)
3	**7**	SL-W006-1	EtOH	50	28	3	2	—	5 (*S*)
4	**7**		*i*PrOH	—	100	99	0	—	53 (*R*)
5	**8**	SL-W008-1	2-Methyl-butan-2-ol	50	96	27	60	—	83 (*R*)
6	**8**		MeOH/H_2O	50	97	51	35	9	71 (*R*)
7	**8**	SL W002-1	*i*PrOH/H_2O	50	86	25	56	3	56 (*R*)
8	**8**		MeOH	—	100	85	3	8	80 (*R*)

[a] **7** or **8**/[Rh(OH)(COD)]$_2$/ligand/Cs_2CO_3: 80/1/1/50; P_{H2} = 100 bar, room temperature; 17 h, reaction time not optimized.
[b] Determined by GC analysis.
[c] Determined by HPLC analysis.

(chemoselectivity and enantioselectivity). Research is currently underway to apply such catalytic systems to the hydrogenation of other heteroaromatic substrates.

4. Experimental

4.1. General and materials

The conversions of the substrates and selectivities were determined by GC analysis on a capillary CP Sil 5CB column (25 m, N_2 = 1 mL/min, 120–250 °C, oven rise = 10 °C/min). The enantiomeric excesses were determined by HPLC analysis using a Chiralpak AD column (hexane/*i*PrOH = 90/10, flow = 0.8 ml/min). All the hydrogenation experiments were prepared under a nitrogen atmosphere. Propan-2-ol and MeOH were degassed with nitrogen prior to use. The 1-*tert*-butyl 2-methyl 1*H*-indole-1,2-dicarboxylate **1** was prepared according to a reported procedure.[4a] The same procedure was used for the ethyl **7**[11] and *tert*-butyl **8** ester.

4.2. General procedure for the catalytic asymmetric hydrogenation of 1-*tert*-butyl 2-methyl 1*H*-indole-1,2-dicarboxylate 1

A 50 ml Schlenk flask equipped with a magnetic stirrer bar was charged with [Rh(OH)(COD)]$_2$ (2.8 mg; 6.25×10^{-3} mmol) and a selected chiral ligand (12.5×10^{-3} mmol). Then the mixture was degassed by three vacuum/N_2 cycles and the degassed solvent (15 ml) was added. The mixture with the precatalyst was stirred at room temperature for 1 h before cannula transfer into a 50 ml double-walled stainless steel autoclave containing substrate **1** (0.96 mmol) and Cs_2CO_3 (202 mg; 0.614 mmol). The autoclave was purged and pressurized with molecular hydrogen and the reaction was performed at the specified temperature over 17 h.

4.3. Di-*tert*-butyl 1*H*-indole-1,2-dicarboxylate 8

Synthesized according to the procedure described by Kuwano et al.[5a] White-beige solid; ^{1}H NMR (300 MHz, $CDCl_3$) 1.60 (s, 9H), 1.65 (s, 9H), 7.23 (m, 1H), 7.38 (m, 1H), 7.58 (m, 1H), 8.03 (m, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) 27.9, 28.2, 81.90, 84.40, 114.73, 114.85, 122.09, 123.10, 126.53, 127.52, 132.22, 137.87, 149.44, 160.67 ppm.

4.4. Di-*tert*-butyl indoline-1,2-dicarboxylate 8a

^{1}H NMR (300 MHz, $CDCl_3$) 1.45 (s, 9H), 1.46 (s, 9H), 2.95 (m, 1H), 3.40 (m, 1H), 4.79 (m, 1H), 7.22 (m, 1H), 7.34 (m, 1H), 7.55 (m, 1H), 7.99 (m, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) 27.97, 28.31, 43.47, 60.76, 81.20, 81.55, 114.59, 122.39, 125.10, 127.89, 128.10, 132.24, 151.80, 170.99 ppm.

Acknowledgments

This work was supported by the Oril Industries (A. M. Maj). The authors thank G. Servant, J.-P. Lecouve, N. Pinault, and M. Sawamura for the fruitful discussions.

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