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Ruthenium-Catalyzed Asymmetric Hydrogenation of *N*-Boc-Indoles

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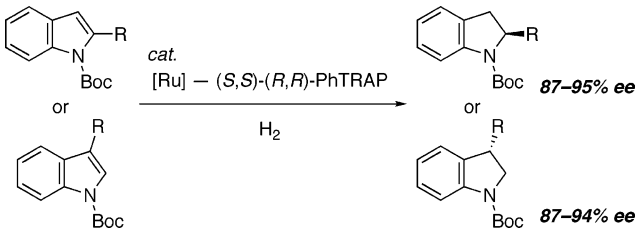
ABSTRACT



Highly enantioselective hydrogenation of various *N*-Boc-indoles proceeded successfully in the presence of the ruthenium complex generated from an appropriate ruthenium precursor and a *trans*-chelate chiral bisphosphine PhTRAP. Various 2- or 3-substituted indoles were converted into chiral indolines with high enantiomeric excesses (up to 95% ee). The PhTRAP–ruthenium catalyst was able to promote the hydrogenation of 2,3-dimethylindoles, giving *cis*-2,3-dimethylindolines with 72% ee.

Catalytic asymmetric hydrogenation is now regarded as a powerful method for the preparation of optically active compounds.[1] The asymmetric catalysis has been used to prepare a variety of optically active molecules from prochiral olefins, ketones, and imines. Meanwhile, asymmetric hydrogenation of heteroaromatics is rare, although the stereoselective transformation will be useful for the construction of optically active heterocyclic skeletons.[2] 2-Methylquinoxaline,[3] 2-alkylquinolines,[4] and pyridines[5,6] have been successfully hydrogenated with over 90% ee to date. Additionally, we accomplished the highly enantioselective hydrogenation of indoles with a rhodium complex modified with PhTRAP (Figure 1),[7] a chiral bisphosphine ligand that is able to form a *trans*-chelate complex with a transition-metal atom.[8]

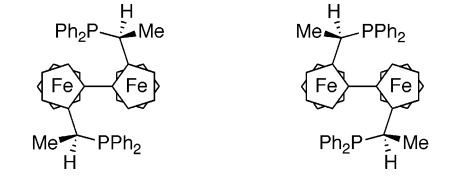


Figure 1. Structure of (*S*,*S*)-(*R*,*R*)- and (*R*,*R*)-(*S*,*S*)-PhTRAP.

This paper describes a new chiral ruthenium catalyst for the asymmetric hydrogenation of indoles. The ruthenium

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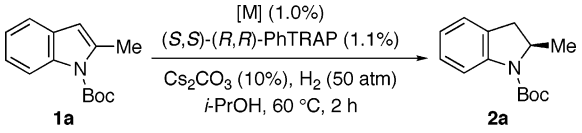
catalyst bearing a PhTRAP ligand converted *N*-Boc-protected (Boc = *tert*-butoxycarbonyl) indoles into chiral indolines with high enantiomeric excess. In general, the Boc group is readily attached to an indole substrate and detached from an indoline product.[9] In our earlier work, the PhTRAP−rhodium-catalyzed hydrogenation required an *N*-acetyl or *N*-sulfonyl protective group to achieve high stereoselectivity.[7]

Asymmetric hydrogenation of *N*-Boc-2-methylindole (**1a**) was attempted with the (*S*,*S*)-(*R*,*R*)-PhTRAP−rhodium−Cs_2CO_3 catalyst system (Table 1, entry 1), but the desired chiral indoline **2a** was obtained with 78% ee (*R*).[7c] To improve enantioselectivity, a variety of catalyst precursors were evaluated for the reaction of **1a** as summarized in Table 1. Use of rhodium catalyst precursors other than $[Rh(nbd)_2]SbF_6$ provided (*R*)-**2a** with 71−78% ee (e.g., entry 2). When $[Ir(cod)Cl]_2$ was used as a catalyst precursor, *S*-enriched **2a** was obtained with 28% ee in low yield (entry 3). Palladium, molybdenum, and tungsten complexes failed to catalyze the hydrogenation of the *N*-Boc-indole. Hydrogenation of **1a** yielded (*R*)-**2a** with 92% ee in the presence of the ruthenium complex generated in situ from $[RuCl_2(p\text{-cymene})]_2$ and PhTRAP (entry 4). The enantiomeric excess of the hydrogenation product was enhanced to 95% when methanol was used in place of 2-propanol (entry 5). The chosen chiral phosphine ligand was crucial for achieving a high yield as well as a high enantiomeric excess of **2a**. The ruthenium complexes prepared from BINAP and DIOP gave a trace of **2a** with 13% and 24% ee, respectively. No hydrogenation of **1a** occurred when most commercially available chiral phosphines were used in place of PhTRAP. In contrast, enantioselectivity was not affected by ligands of ruthenium catalyst precursors. Ruthenium precursors $[RuCl_2(benzene)]_2$ and $Ru(\eta^3\text{-2-methylallyl})_2(cod)$[10] were comparable to $[RuCl_2(p\text{-cymene})]_2$ (entries 6 and 7). Cesium carbonate seemed to act as a base because the hydrogenation product **2a** was quantitatively obtained with 93−95% ee from the reaction using potassium carbonate, triethylamine, or 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in place of cesium carbonate. The PhTRAP−$[RuCl_2(p\text{-cymene})]_2$ complex did not work well as a chiral catalyst for the asymmetric hydrogenation in the absence of base (entry 8).

The reaction of $[RuCl_2(p\text{-cymene})]_2$ with (*S*,*S*)-(*R*,*R*)-PhTRAP yielded a brown amorphous solid containing a single ruthenium species. The structure of the ruthenium complex was supposed to be [RuCl(*p*-cymeme){(*S*,*S*)-(*R*,*R*)-PhTRAP}]Cl (**3**) by analogy with the reaction of $[RuCl_2(arene)]_2$ and other bisphosphines.[11] The ^{1}H NMR spectrum of the complex indicated that one *p*-cymene and one PhTRAP were bound to ruthenium. The ^{31}P NMR of the ruthenium complex showed a pair of doublet peaks at 9.0 and 25.1 ppm with a J_{P-P} value of 42 Hz.[12] The isolated PhTRAP−ruthenium complex **3** exhibited catalytic activity and stereoselectivity at the same level as the in-situ-generated ruthenium catalyst (Table 2, entry 1).

As shown in Table 2, a wide range of 2-substituted *N*-Boc-indoles were hydrogenated with high enantioselectivity by

Table 1. Screening of Catalysts for Asymmetric Hydrogenation of **1a**[a]

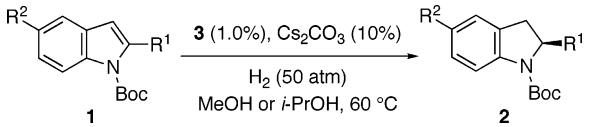


1a **2a**

entry	[M]	yield, %[b]	ee, %[c]
1	$[Rh(nbd)_2]SbF_6$	100	78 (*R*)
2	$[RhCl(cod)]_2$	100	73 (*R*)
3	$[IrCl(cod)]_2$	14	28 (*S*)
4	$[RuCl_2(p\text{-cymene})]_2$	100	92 (*R*)
5[d]	$[RuCl_2(p\text{-cymene})]_2$	100	95 (*R*)
6[d]	$[RuCl_2(benzene)]_2$	100	96 (*R*)
7[d]	$Ru(\eta^3\text{-2-methylallyl})_2(cod)$	100	95 (*R*)
8[d,e]	$[RuCl_2(p\text{-cymene})]_2$	7	63 (*R*)

[a] Reactions were conducted on a 0.5 mmol scale in 1.0 mL of 2-propanol. [b] Determined by ^{1}H NMR analysis of crude product. [c] Determined by chiral HPLC. [d] The reactions were conducted in methanol. [e] The reaction was conducted without Cs_2CO_3.

Table 2. Catalytic Asymmetric Hydrogenation of 2-Substituted Indoles **1**[a]



1 **2**

entry	R^1	R^2	**1**	time, h	**2**	yield, %[b]	ee, %[c]
1	Me	H	**1a**	2	**2a**	99	95
2	Me	OMe	**1b**	2	**2b**	97	91
3	Me	F	**1c**	2	**2c**	96	90
4[d]	Bu	H	**1d**	2	**2d**	94	92
5[d,e]	*c*-C_6H_{11}	H	**1e**	48	**2e**	92	87
6[d,e]	Ph	H	**1f**	24	**2f**	99	95
7[e]	C_6H_4-*p*-F	H	**1g**	4	**2g**	95	93
8[e]	CO_2Me	H	**1h**	2	**2h**	91	90

[a] Reactions were conducted on a 0.5 mmol scale in 1.0 mL of methanol. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reactions were conducted in the presence of the enantiomeric catalyst [RuCl(*p*-cymene){(*R*,*R*)-(*S*,*S*)-PhTRAP}]Cl (**3′**). [e] The reactions were conducted in 2-propanol.

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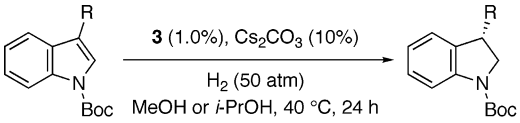
the chiral ruthenium catalyst **3**. Neither electron-donating nor -withdrawing substituents at the 5-position of **1** caused a significant decrease in the enantiomeric excess of the hydrogenation product **2** (entries 2 and 3). The enantioselectivity was scarcely affected by the substituent at the 2-position. Indoles **1d**−**h** bearing primary and secondary alkyl, aryl, or ester groups were transformed into the desired indolines **2d**−**h** with 87−95% ee (entries 4−8). Of note, 2-cyclohexylindoline **2e** was obtained with 87% ee in high yield. The PhTRAP-rhodium catalyst, which was developed by us previously, failed to promote the hydrogenation of 2-cyclohexylindole.[7c] However, no hydrogenation of 2-(*tert*-alkyl)indole occurred with the ruthenium catalyst.

The chiral catalyst **3** is effective for the asymmetric reductions of 3-substituted *N*-Boc-indoles **4** as well as **1** (Scheme 1). The hydrogenation of 3-methylindole **4a** yielded

Scheme 1. Catalytic Asymmetric Hydrogenation of 3-Substituted Indoles **4**



4a: R = Me
4b: R = Ph

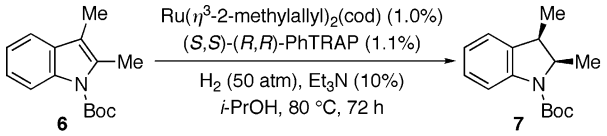
5a: R = Me (92%, 87% ee)
5b: R = Ph (85%, 94% ee)

(*S*)-3-methylindoline **5a** with 87% ee. The stereochemistry of the product indicates that the hydrogen delivery occurs from the *re* face of the alkene which is opposite to what is observed in the case of **1**. Similarly, optically active 3-phenylindoline **5b** was obtained with 94% ee.

Furthermore, the asymmetric hydrogenation of 2,3-disubstituted indole **6** was attempted using the PhTRAP−ruthenium catalyst (Scheme 2). The reaction can create two vicinal chiral centers simultaneously. No formation of **7** was

(12) The coupling constant indicates that PhTRAP coordinates the ruthenium in a cis chelation manner. The cis geometry of the two phosphoruses of PhTRAP may be enforced by the η^6-arene ligand of **3**. The arene ligand would be liberated from the ruthenium on starting the asymmetric hydrogenation; therefore, the geometry of PhTRAP would be kept trans during the reaction.

Scheme 2. Catalytic Asymmetric Hydrogenation of 2,3-Dimethylindole **6**



59%, 72% ee (−)

observed when the PhTRAP−rhodium complex was used as a catalyst. In contrast, ruthenium catalyst **3** promoted the hydrogenation of **6**, resulting in 50% yield of *cis*-2,3-dimethylindoline (−)-**7** with 65% ee. No diastereomer of **7** was detected in the reaction mixture by ^{1}H NMR. The ee value of **7** was improved to 72% using the PhTRAP−ruthenium catalyst generated in situ from Ru(η^3-2-methylallyl)$_2$-(cod).

We have developed a new chiral ruthenium catalyst **3** for the asymmetric hydrogenation of indoles. When the PhTRAP ligand was replaced with other phosphine ligands, the ruthenium catalyst failed to give the hydrogenation product. The present ruthenium catalyst enabled highly enantioselective hydrogenation of various *N*-Boc-protected indoles to give chiral indolines which are useful chiral synthons in organic synthesis. Moreover, the hydrogenation of a 2,3-disubstituted indole proceeded successfully with significant enantioselectivity using the PhTRAP−ruthenium catalyst.

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

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