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Highly Enantioselective Synthesis of Chiral 3-Substituted Indolines by Catalytic Asymmetric Hydrogenation of Indoles

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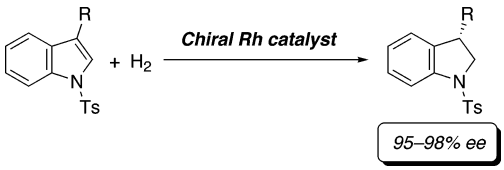
ABSTRACT



***N*-Tosyl 3-substituted indoles were hydrogenated with high enantioselectivities (95–98% ee) by use of a trans-chelating chiral bisphosphine, (*S*,*S*)-(*R*,*R*)-PhTRAP ligand. The chiral catalyst, which was generated in situ from [Rh(nbd)$_2$]SbF$_6$, PhTRAP, and Cs_2CO_3, is useful for enantioselectively synthesizing a range of diverse optically active indolines possessing a chiral carbon at the 3-position.**

The highly enantioselective hydrogenation of heteroaromatics could offer a straightforward approach to a wide range of optically active heterocycles if it could be performed successfully on a routine basis. However, the heteroaromatic substrates applicable to asymmetric reduction have so far been limited to 2-methylquinoxaline,[1] 2-substituted quinolines,[2,3] and 2-substituted indoles.[4]

Notwithstanding 3-substituted indolines being important chiral constituents of a number of biologically active compounds (e.g., the Duocarmycins),[5,6] methods for the enantioselective formation of a chiral center at the 3-position have been scarce. Recently, Groth and Bailey reported the stereoselective syntheses of chiral 3-substituted indolines by asymmetric intramolecular carbolithiation.[7−9] This methodology suffers several disadvantages in that it requires an excess of chiral agent to deliver chiral products that never exceed 90% ee.

Recently, we reported the first highly enantioselective hydrogenation of 2-substituted *N*-acetylindoles.[4] A rhodium complex bearing a trans-chelating chiral bisphosphine PhTRAP[10−12] (Figure 1) was the most enantioselective catalyst. It afforded optically active indolines bearing a chiral

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

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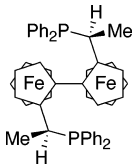
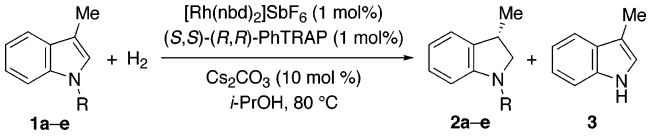


Figure 1. Structure of (*S*,*S*)-(*R*,*R*)-PhTRAP.

carbon at the 2-position with up to 95% ee. In this paper we now describe a new highly enantioselective synthesis of 3-substituted indolines that also proceeds by asymmetric hydrogenation with the PhTRAP−rhodium catalyst. The enantiomeric excesses of the products were between 93 and 98%.

First, we attempted the asymmetric hydrogenation of *N*-acetyl-3-methylindole (**1a**) in 2-propanol at 50 atm of hydrogen pressure in the presence of the (*S*,*S*)-(*R*,*R*)-PhTRAP-[Rh(nbd)$_2$]SbF$_6$-Cs$_2$CO$_3$ (nbd = 2,5-norbornadiene) catalyst, which is the most effective for achieving the asymmetric hydrogenation of 2-substituted indoles.[4] Through this reaction, it was possible to obtain 3-methylindoline (*S*)-**2a** with 84% ee in 24% yield. However, the majority (58%) of **1a** that remained underwent undesirable alcoholysis of the *N*-acetyl group under these conditions. Thus, our initial effort focused on controlling the undesirable solvolysis. The use of weak or insoluble bases (Et$_3$N, Na$_2$CO$_3$, etc.) did suppress this side reaction, but the ee values of the resulting products were lower than 10%. No hydrogenation occurred in MeCN, THF, or toluene. Next, we evaluated a variety of protective groups on the nitrogen of **1** (Table 1). Although

Table 1. Catalytic Asymmetric Hydrogenation of 3-Methylindoles[a]



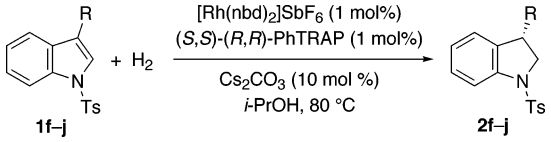
		conversion, %[b]	yield, %[b]		ee, %[c]
entry	R (**1**)	**1**	**2**	**3**	**2**
1	Ac (**1a**)	82	24	58	84
2[d]	Boc (**1b**)	14	14	0	16
3	Ts (**1c**)	31	31	0	97
4[e]	Ts (**1c**)	100	100 (96)	0	98
5[e]	Ms (**1d**)	95	92 (83)	3	94
6[e]	Tf (**1e**)	100	100 (93)	0	94

[a] Reactions were conducted at 80 °C and 50 atm of H_2 in 2-propanol (2 mL) for 2 h unless otherwise specified. **1** (0.5 mmol)/[Rh(nbd)$_2$]SbF$_6$/(*S*,*S*)-(*R*,*R*)-PhTRAP/Cs$_2$CO$_3$ was 100/1.0/1.0/10. [b] Determined by ^{1}H NMR analysis. Isolated yields are given in parentheses. [c] Determined by chiral HPLC analysis. [d] Reaction was conducted at 100 atm of H_2. [e] Reactions were conducted for 24 h.

no solvolysis of the *tert*-butoxycarbonyl group of **1b** was observed in the presence of Cs$_2$CO$_3$, the enantiomeric excess of **2b** was found to be only 16% (entry 2). We then discovered that hydrogenation of *N*-sulfonylindoles **1c**−**e** proceeded with high enantioselectivity and acceptable reaction rates (entries 3−6). In particular, the reaction of *N*-tosylamide **1c** produced 98% ee of (*S*)-3-methyl-*N*-tosylindoline (**2c**) in 96% isolated yield after 24 h with no formation of **3** (entry 4).[13] Similarly, when the (*R*,*R*)-(*S*,*S*)-PhTRAP ligand was used, the antipode (*R*)-**2c** was obtained with 98% ee. The *N*-tosyl group of **2c** was removable by reduction using sodium bis(2-methoxyethoxy)aluminum dihydride without the loss of enantiopurity.[14] It is noteworthy that no hydrogenation occurred in the presence of rhodium complexes generated from other phosphine ligands, e.g., PPh$_3$ and cis-chelating bisphosphine BINAP.[15]

As seen from Table 2, a variety of 3-substituted *N*-tosylindolines could be obtained with high enantiomeric

Table 2. Catalytic Asymmetric Hydrogenation of 3-Substituted Indoles[a]



entry	R (**1**)	yield (**2**), %	ee, %
1[d]	*i*-Pr (**1f**)	94 (**2f**)	97
2[e]	Ph (**1g**)	93 (**2g**)	96
3	CH_2CH_2OTBS (**1h**)	94 (**2h**)	98
4	$CH_2CH_2CO_2$(*t*-Bu) (**1i**)	93 (**2i**)	97
5	CH_2CH_2NHBoc (**1j**)	71 (**2j**)	95

[a] Reactions were conducted at 80 °C and 50 atm of H_2 in 2-propanol (2.0 mL) for 24 h. **1** (0.5 mmol)/[Rh(nbd)$_2$]SbF$_6$/(*S*,*S*)-(*R*,*R*)-PhTRAP/Cs$_2$CO$_3$ was 100/1.0/1.0/10 unless otherwise specified. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Reaction was conducted in 2-propanol (1.0 mL) for 48 h. [e] Performed with 2 mol % PhTRAP−Rh catalyst.

excesses and high yields by asymmetric hydrogenation with the PhTRAP−rhodium catalyst. The indoles **1f** and **1g** bearing bulky substituents at the 3-position underwent highly enantioselective hydrogenation (entries 1 and 2). Silyl ether, ester, and carbamate groups did not cause a significant deterioration in stereoselectivity (entries 3−5). No hydrogenation of *tert*-butyl (3-indolyl)acetate occurred by means of the present catalyst system. Its enolizable hydrogens may cause deactivation of the catalyst.

Next, we applied our enantioselective hydrogenation method to the catalytic asymmetric synthesis of chiral indoline **4** (Scheme 1). This compound is Wierenga's synthetic intermediate for the left-hand segment of the antitumor agent (+)-

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(13) See Supporting Information for assignment of absolute configuration of **2c**.
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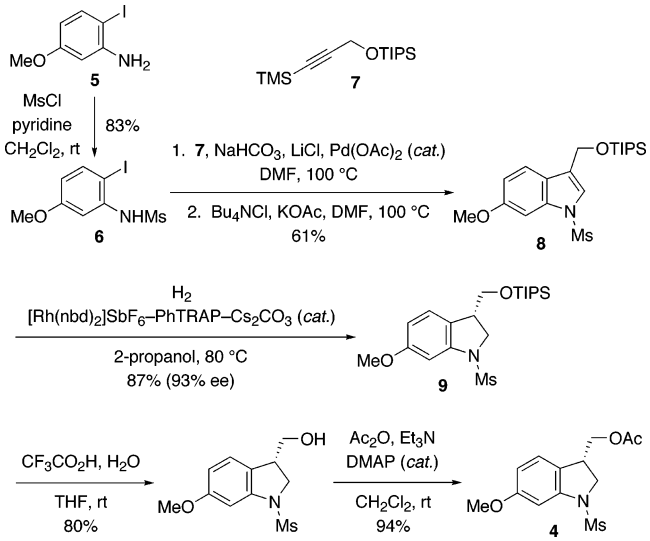
(15) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl

Scheme 1. Catalytic Asymmetric Synthesis of **4**



CC-1065, although the compound was previously synthesized in racemic form.[16] After N-mesylation of 2-iodo-5-methoxyaniline (**5**),[17] the resulting sulfonamide **6** was subjected to palladium-catalyzed intermolecular annulation with silylacetylene **7**,[18] and it was transformed into the indole having a trimethylsilyl group at the 2-position. The 2-silyl group of the indole was removed selectively by exposure to Bu_4NCl and KOAc in DMF at 100 °C. The indole **8** was reduced to the chiral indoline **9** in 93% ee using the present catalytic asymmetric hydrogenation method with (*S*,*S*)-(*R*,*R*)-PhTRAP. After changing the TIPS protection of **9** into the acetate, the desired indoline **4** was obtained in optically active form.

In summary, we have developed a new highly enantioselective approach to chiral 3-substituted indolines by way of catalytic asymmetric reduction of indoles. The use of the trans-chelating chiral diphosphine PhTRAP is essential for the occurrence of hydrogenation, as well as for achieving high enantioselectivity. This methodology is applicable to the preparation of a wide range of optically active indolines having a chiral center at the 3-position.

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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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