Asymmetric Catalysis

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Asymmetric Hydrogenation of Azaindoles: Chemo- and Enantioselective Reduction of Fused Aromatic Ring Systems Consisting of Two Heteroarenes

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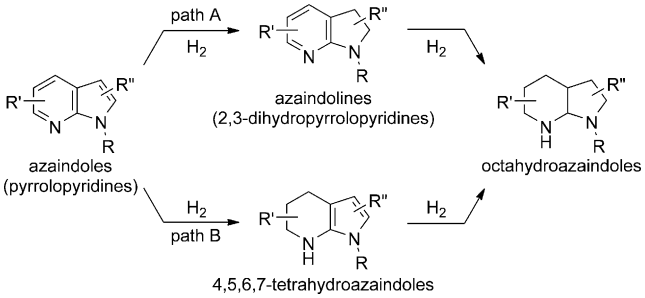
Abstract: *High enantioselectivity was achieved for the hydrogenation of azaindoles by using the chiral catalyst, which was prepared from [Ru(η^3-methallyl)$_2$(cod)] and a trans-chelating bis(phosphine) ligand (PhTRAP). The dearomative reaction exclusively occurred on the five-membered ring, thus giving the corresponding azaindolines with up to 97:3 enantiomer ratio.*

Asymmetric hydrogenation of heteroarenes is a promising method for organic synthesis. The reaction directly transforms heteroaromatic substrates into chiral heterocycles, which are often seen in useful organic molecules.[1] In the last decade, much effort has been devoted to developing the asymmetric transformation. Various heteroarenes have been hydrogenated to the corresponding heterocycles in high enantioselectivity through asymmetric catalysis.[2–8] Meanwhile, asymmetric hydrogenation of fused aromatic rings consisting of two (or more) heteroarenes is still severely limited in scope because of the complexity arising from chemoselectivity. The asymmetric hydrogenations of indolizines[9] and pyrrolo[1,2-*a*]pyrazinium salts[10] have been reported. In these works, the reductions selectively took place on the six-membered rings. Fan and co-workers successfully developed the highly enantioselective hydrogenation of 2,6-disubstituted 1,5-naphthyridines.[11,12] Moderate to low site selectivities, however, were observed when naphthyridines were unsymmetrically substituted with small electronic biases.

We focused on the asymmetric hydrogenation of pyrido-fused pyrroles, azaindoles. To develop the hydrogenation, two possible reaction pathways, paths A and B, should be considered (Scheme 1). Path A starts from the addition of H_2 to the C2–C3 double bond, thus leading to the formation of an azaindoline. In path B, the pyridine ring is preferentially reduced to give 4,5,6,7-tetrahydroazaindoles. Moreover, these two possible products may be further hydrogenated to give octahydroazaindoles. The fully saturated products as well as the partially reduced azaindoles are important as biologically active compounds,[13a–c] ligands in metal complexes,[13d] etc.[13e] Herein, we describe the ruthenium-catalyzed asymmetric hydrogenation of azaindoles. The hydrogenation occurred



Scheme 1. Supposed pathways for the hydrogenation of azaindoles.

selectively on the pyrrole ring to afford azaindolines with up to 97:3 enantiomer ratio (e.r.).

Initial attempts on the catalytic asymmetric hydrogenation of azaindoles were performed using the 2-methyl-7-azaindole **1aa** as the benchmark substrate (Table 1). Exclusive reduction of the pyrrole ring was observed in the hydrogenation using a [Rh(nbd)$_2$]$^+$/PhTRAP catalyst (Figure 1), which is useful for the asymmetric hydrogenation of indoles (Table 1, entry 1).[2a,b] However, the azaindoline

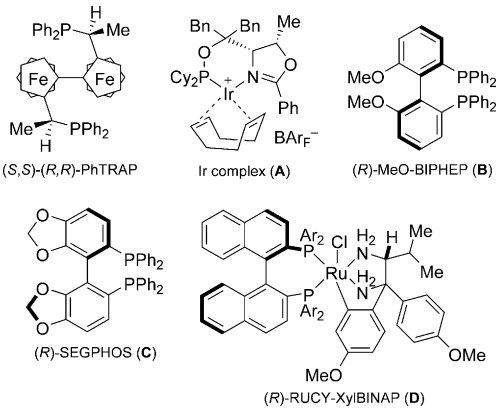


Figure 1. Chiral ligands and catalysts used in Table 1.

2aa was obtained in low yield and its e.r. value was moderate. Use of a [Ru(η^3-methallyl)$_2$(cod)]/PhTRAP catalyst[2c] led to the remarkable improvement of the yield as well as the enantioselectivity (entry 2).[14] However, the hydrogenation competed with the solvolysis of the Boc group of **1aa**. The undesired reaction caused a significant decrease in the yield of **2aa**. Furthermore, the hydrogenation was attempted with some other chiral catalysts, which have been employed for the

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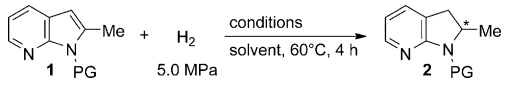
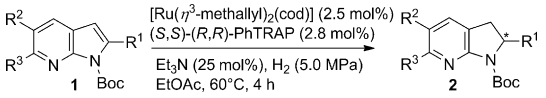
Table 1: Optimization study.[a]



Entry	PG	Conditions	Solvent	Conv. [%][b]	Yield [%][c]	e.r.[d]
1	Boc (**1aa**)	[Rh]/PhTRAP Cs_2CO_3[e]	*i*PrOH	10	5[b,f]	81:19
2	Boc (**1aa**)	[Ru]/PhTRAP Cs_2CO_3[g]	MeOH	100	47[h]	93:7
3[j]	Boc (**1aa**)	Ir complex (**A**)[j]	CH_2Cl_2	<5	–	–
4	Boc (**1aa**)	[Ir]/**B**, I_2[j,k]	toluene	<5	–	–
5	Boc (**1aa**)	[Ir]/**C** $ClCO_2Me/Li_2CO_3$[j,l]	THF	<5	–	–
6	Boc (**1aa**)	Ru complex (**D**) KO*t*Bu[j,m]	toluene	<5	–	–
7	Boc (**1aa**)	[Ru]/PhTRAP[n]	EtOAc	100	98	94:6
8	Ts (**1ab**)	[Ru]/PhTRAP[n]	EtOAc	100	86	77:23
9	Me (**1ac**)	[Ru]/PhTRAP[n]	EtOAc	<5	–	–
10	H (**1ad**)	[Ru]/PhTRAP[n]	EtOAc	<5	–	–

[a] Unless otherwise noted, reactions were conducted on a 0.20 mmol scale with 2.5 mol% catalyst loading in 1.0 mL of solvent under 5.0 MPa of H_2 at 60°C for 4 h. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of the isolated product **2**. [d] Determined by HPLC analysis. [e] $[Rh(nbd)_2]SbF_6$/PhTRAP/Cs_2CO_3 = 1.0:1.1:10. [f] **1ad** was formed in 5% yield (^{1}H NMR). [g] [Ru(η^3-methallyl)$_2$(cod)]/PhTRAP/Cs_2CO_3 = 1.0:1.1:10. [h] **1ad** was formed in 50% yield (^{1}H NMR). [i] Under 7.5 MPa of H_2 at RT for 24 h. [j] With 1.0% catalyst loading. [k] [{IrCl(cod)}$_2$]/**B**/I_2 = 0.5:1.1:10. [l] [{IrCl(cod)}$_2$]/**B**/$ClCO_2Me$/Li_2CO_3 = 0.5:1.1:110:120. [m] **D**/KO*t*Bu = 1.0:4.5. [n] [Ru(η^3-methallyl)$_2$(cod)]/PhTRAP = 1.0:1.1. Boc = *tert*-butoxycarbonyl, cod = 1,5-cyclooctadiene, nbd = norbornadiene, PG = protecting group, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

Table 2: Enantioselective hydrogenation of 7-azaindoles.[a]



Entry	R^1	R^2	R^3	1	2	Conv. [%][b]	Yield [%][c]	e.r.[d]
1[e]	Me	H	H	**1aa**	**2aa**	100	98	94:6
2	*n*Hex	H	H	**1b**	**2b**	100	98	88:12
3	*i*Bu	H	H	**1c**	**2c**	80	71	77:23
4	*c*Hex	H	H	**1d**	**2d**	<5	–	–
5	Ph	H	H	**1e**	**2e**	17	10	96:4
6[f,g]	Ph	H	H	**1e**	**2e**	84	77	97:3
7[f]	4-$MeOC_6H_4$	H	H	**1f**	**2f**	67	59	97:3
8[f]	4-$CF_3C_6H_4$	H	H	**1g**	**2g**	60	56	91:9
9[e]	CO_2Et	H	H	**1h**	**2h**	100	96	97:3
10[e]	Me	Me	H	**1i**	**2i**	87	81	91:9
11[e]	Me	F	H	**1j**	**2j**	100	93	84:16
12[e]	Me	CF_3	H	**1k**	**2k**	88	79	81:19
13[e]	Me	H	Me	**1l**	**2l**	100	85	93:7

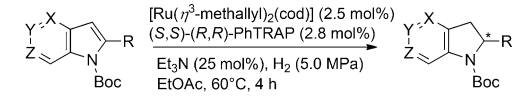
[a] Unless otherwise noted, reactions were conducted on a 0.20 mmol scale in 1.0 mL of EtOAc under 5.0 MPa of H_2 at 60°C for 4 h. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of the isolated product **2**. [d] Determined by HPLC analysis. [e] Without Et_3N. [f] In toluene at 40°C for 48 h. [g] 10.0 MPa of H_2.

enantioselective hydrogenation of indoles[2d] and benzo-fused azines,[4a,b,6e] but reduction of neither the five- nor six-membered ring was observed (entries 3–6). The undesired solvolysis was completely suppressed by use of aprotic EtOAc solvent, which led to the quantitative formation of **2aa** (entry 7). The N-substituent of the azaindole **1** remarkably impacted the stereoselectivity as well as the reactivity (entries 8–10). The PhTRAP/ruthenium catalyst could produce the *N*-tosylazaindoline **2ab** in high yield, but its e.r. value was moderate (entry 8). The methyl-substituted and nonsubstituted azaindoles, **1ac** and **1ad**, did not react under the ruthenium-catalyzed hydrogenation conditions (entries 9 and 10).

Various 2-substituted 7-azaindoles (**1**) were transformed into the chiral azaindolines **2** in good to high enantioselectivities (Table 2). The PhTRAP/ruthenium catalyst hydrogenated the azaindoles bearing a primary alkyl (R^1; entries 2 and 3). However, the bulkiness of R^1 significantly affected the enantioselectivity as well as the reaction rate. The products **2b** and **2c** were obtained with 88:12 and 77:23 e.r. values, respectively. The larger cyclohexyl group of **1d** hampered the ruthenium catalysis (entry 4). At 60°C in EtOAc, the reaction of the 2-phenyl-7-azaindole **1e** led to **2e** with high stereoselectivity, but the yield of **2e** was low (entry 5). Prolonging the reaction time failed to improve the reaction (19% for 72 h). In the early stage of the hydrogenation, trace amounts of **1e** decomposed into its free azaindole (less than 10%), which might inhibit the ruthenium catalysis. To avoid the decomposition, the hydrogenation of **1e** was carried out in toluene at lower temperature. The mild reaction conditions allowed the hydrogenation to produce 2-aryl-7-azaindolines with high e.r. values in moderate yields (entries 6–8). The electron-donating group on the aryl substituent was preferable to the electron-withdrawing one. The azaindolecarboxylate **1h** was quantitatively transformed into **2h** with 97:3 e.r. (entry 9). To our surprise, the enantioselectivity was significantly affected by the electronic properties of the 5-substituent, even though it was located far from the reaction site (entries 10–12). The position of the substituent scarcely influenced the asymmetric catalysis as compared with the electronic effect (entries 10 and 13).

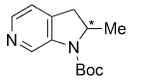
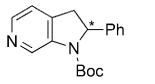
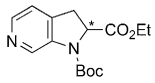
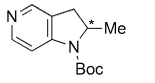
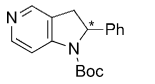
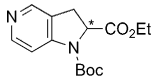
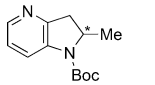
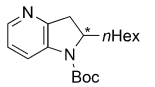
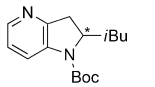
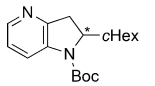
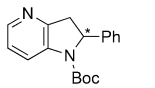
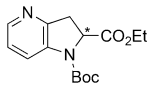
A series of 6-, 5-, and 4-azaindoles were also transformed into azaindolines by the PhTRAP/ruthenium catalyst (Table 3). The position of the nitrogen atom modestly affected the enantioselectivity in the reactions of 2-methylazaindoles (entries 1, 4, and 7). In the case of 2-phenylazaindoles, the reaction of 6- and 5-azaindoles, **3b** and **5b**, proceeded with stereoselectivities comparable to that of **1e** (entries 2 and 5). However, **7e** was reduced with moderate e.r. values (entry 11). As with 2-phenylazaindoles, the 4-azaindole-2-carboxylate **7f** was hydrogenated with lower enantioselectivity than **3c** and **5c** (entries 3, 6, and 12). The correlation between the e.r. value and the size of the 2-substituent in the 4-azaindoles **7** is similar to that observed for the 7-azaindoles **1** (entries 7–10).

Table 3: Enantioselective hydrogenation of 6-, 5-, and 4-azaindoles.[a]



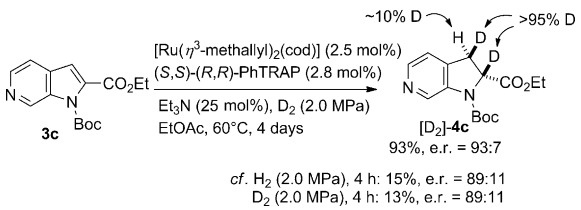
X=CH, Y=CH, Z=N (**3**)
X=CH, Y=N, Z=CH (**5**)
X=N, Y=CH, Z=CH (**7**)

X=CH, Y=CH, Z=N (**4**)
X=CH, Y=N, Z=CH (**6**)
X=N, Y=CH, Z=CH (**8**)

Entry	Substrate	Product		Conv. [%][b]	Yield [%][c]	e.r.[d]
1[e]	**3a**		**4a**	100	98	91:9
2[f]	**3b**		**4b**	90	86	94:6
3	**3c**		**4c**	100	90	91:9
4	**5a**		**6a**	100	94	95:5
5[f]	**5b**		**6b**	87	81	92:8
6	**5c**		**6c**	100	82	92:8
7[e]	**7a**		**8a**	100	99	93:7
8	**7b**		**8b**	100	99	79:21
9	**7c**		**8c**	100	89	77:23
10	**7d**		**8d**	< 5	–	–
11[f]	**7e**		**8e**	75	68[b]	83:17
12[g]	**7f**		**8f**	100	85	75:25

[a] Unless otherwise noted, reactions were conducted on a 0.20 mmol scale in 1.0 mL of EtOAc under 5.0 MPa of H_2 at 60 °C for 4 h. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of isolated product. [d] Determined by HPLC analysis. [e] Without Et_3N. [f] In toluene at 40 °C for 48 h. [g] At 100 °C.

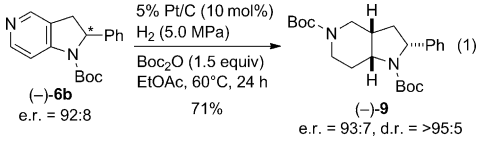
To shed light on the mechanism of the hydrogenation of azaindoles, the deuteration of **3c** was carried out under 2.0 MPa of D_2 (Scheme 2). The deuterium atoms were incorporated into the azaindoline product [D_2]-**4c** through a *syn*-addition.[15] This observation suggests that the hydrogenation proceeds through the following mechanism: the addition of a ruthenium hydride species to the C2–C3 moiety of azaindole with either subsequent reductive elimination or the σ-bond metathesis with H_2 to form the azaindoline. Furthermore, the labelling experiment ruled out the isomerization of a alkylruthenium intermediate and the pathway

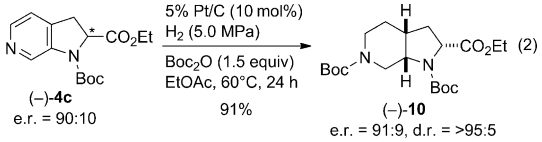


Scheme 2. Deuterium-labeling experiment.

involving the hydrogenation of the C–N double bond in the iminium tautomer of the azaindole.[2e,g] To our surprise, the deuteration of **3c** gave [D_2]-**4c** in a yield comparable to that of the corresponding hydrogenation. The small kinetic isotope effect (1.0–1.2) may indicate that the insertion of C2–C3 double bond into Ru–H bond is the turnover-limiting step. A similar kinetic isotope effect had been reported in the rhodium-catalyzed hydrogenation of α-acetamidoacrylates.[16]

Finally, we explored the stereoselective hydrogenation of the remaining pyridine rings in the chiral azaindoline products. The octahydroazaindoles with an all-*cis* configuration were selectively obtained by using a Pt/C catalyst in the presence of Boc_2O. Starting from the 5-azaindoline (−)-**6b** with 92:8 e.r., the reduction proceeded to provide (−)-**9** with no loss of the enantiopurity [Eq. (1)]. Under the same reaction conditions, the 6-azaindoline (−)-**4c** was selectively converted into (−)-**10** [Eq. (2)], which may be a useful synthetic intermediate for a specific class of IAP inhibitors.[13b,c]





In summary, we found that the hydrogenation of azaindoles selectively took place on the five-membered ring by using the PhTRAP/ruthenium catalyst. The chiral catalyst allows the hydrogenation to produce optically active azaindolines with up to 97:3 e.r. Use of the *trans*-chelating bis(phosphine) ligand is crucial for the high enantioselectivity as well as the chemoselectivity. Moreover, the azaindoline products are further saturated to the *cis*-octahydroazaindoles without formation of their diastereomers and loss of the enantiopurities.

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Keywords: asymmetric catalysis · azaindoles · chemoselectivity · hydrogenation · ruthenium

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[15] The H at the 3-position of **3c** might be scrambled with deuterium atom through the ruthenium catalysis. When the deuteration stopped at the early stage (4 h), a small amount of H/D scrambling also observed in the recovered starting materials. Moreover, the PhTRAP-ruthenium catalyst is inactive for the dehydrogenation of **4c** to **3c**; see the Supporting Information for more details.

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