Hydrogenation of Five-Membered Heteroaromatic Compounds Catalyzed by a Rhodium-Phosphine Complex

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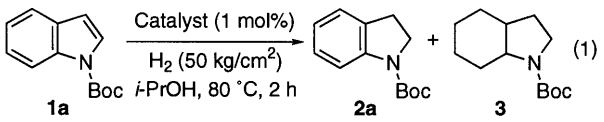
The rhodium complex generated *in situ* from Rh(acac)(cod) and 2 equivalents of triphenylphosphine is an effective catalyst for hydrogenation of various five-membered heteroaromatic compounds.

Hydrogenation of heteroaromatic compounds is a useful reaction to provide saturated or partially unsaturated heterocyclic compounds,[1] whose skeletons are found in many biologically active natural products and medicines.[2] As well, the hydrogenation, which includes hydrodenitrogenation, hydrodeoxygenation, and hydrodesulfurization from petroleum and coal, offers an industrially important process. Although many efforts have been made toward development of the hydrogenation of heteroaromatic compounds using homogeneous catalysis[3–5] which is advantageous to pursuit of stereoselectivity,[6] many shortcomings of the catalysts have thwarted their utilization for organic synthesis, e.g. limitation of substrate, low catalytic activity, and difficulty in the availability and modification of the catalysts. Herein, we report that a rhodium–phosphine complex provided high catalytic activity for hydrogenations of various five-membered heteroaromatic compounds. The rhodium catalyst is readily prepared *in situ* by mixing commercially available Rh(acac)(cod) and triphenylphosphine.

First of all, we examined several transition metal–phosphine complexes for hydrogenation of 1-*tert*-butoxycarbonylindole (**1a**) (eq 1). The reactions were carried out in 2-propanol



(0.5 M) at 80 °C under 50 kg/cm^2 of hydrogen for 2 h. The results are shown in Table 1. Wilkinson complex RhCl(PPh$_3$)$_3$, which is well-known as a catalyst for hydrogenation of various unsaturated compounds, exhibited some catalytic activity for the hydrogenation of **1a** (entry 1). Iridium and ruthenium complexes were also possible to promote the hydrogenation, but much less effective than rhodium catalyst (entries 2 and 3). On further screening of some rhodium complexes, a rhodium complex (1 mol%) generated *in situ* from Rh(acac)(cod) and 2 equivalents of triphenylphosphine was found to be the most effective catalyst, which completes the regioselective hydrogenation within 2 h to give *N*-Boc-indoline **2a** selectively in quantitative GC yield (91% isolated yield) with no detectable by-product (entry 6).[7,8] The high catalytic activity of the rhodium catalyst is demonstrated by completion of hydrogenation of **1a** within 6 h even with 0.1 mol% of the catalyst (92% isolated yield). The catalytic activity is the best in hydrogenations of indoles using homogeneous catalyst to our knowledge.[9,10]

Table 1. Catalytic hydrogenation of *N*-Boc-indole (**1a**)[a]

Entry	Catalyst	Yield/%[b]
1	RhCl(PPh$_3$)$_3$	11
2	1/2 [IrCl(cod)]$_2$–2PPh$_3$	3
3	RuCl$_2$(PPh$_3$)$_3$	3
4	PdCl$_2$(PPh$_3$)$_2$	0
5	[Rh(nbd)$_2$]SbF$_6$–2PPh$_3$	18
6	Rh(acac)(cod)–2PPh$_3$	100
7	Rh(acac)(cod)–1PPh$_3$	83[c]
8	Rh(acac)(cod)–4PPh$_3$	20
9	Rh(acac)(cod)–DPPF[d]	100
10	RhH(PPh$_3$)$_4$	19
11	RhH(CO)(PPh$_3$)$_3$	0

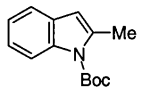
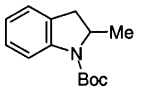
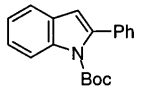
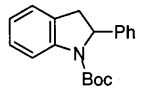
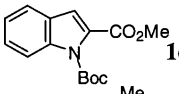
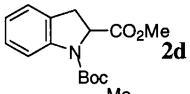
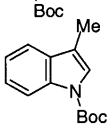
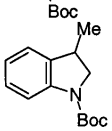
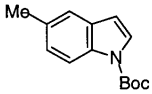
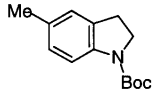
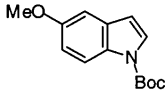
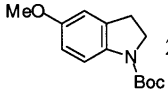
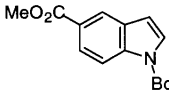
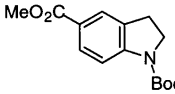
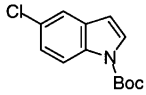
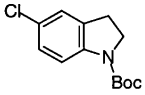
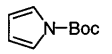
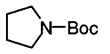
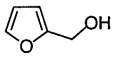
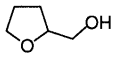
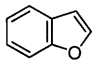
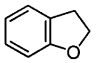
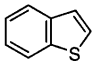
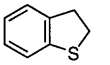
[a]All reactions were carried out in 2-propanol at 80 °C under 50 kg/cm^2 of hydrogen pressure for 2 h. **1a**/catalyst = 100/1. [b]GC yields. [c]17 % of **3a** was produced. [d]DPPF = 1,1'-bis(diphenylphosphino)ferrocene.

Molar equivalent of phosphine to rhodium atom was a crucial factor for the catalytic activity (entries 7 and 8). Lower ratio of phosphine ligand to rhodium (1:1) induced complete hydrogenation of the aryl ring of **1a** to give **3** (17%). On the other hand, higher phosphine ratio caused significant deterioration of the catalytic activity. Bisphosphine ligand, 1,1'-bis(diphenylphosphino)ferrocene (DPPF), can be used instead of triphenylphosphine, exhibiting comparable catalytic activity (entry 9). Active species for the catalytic hydrogenation may be a rhodium(I)–hydride complex generated *in situ* from reaction of (acetylacetonato)rhodium(I) with hydrogen.[11] RhH(PPh$_3$)$_4$ provided the same catalytic activity as Rh(acac)(cod)–4PPh$_3$ (entry 10). However, RhH(CO)(PPh$_3$)$_3$ did not promote the hydrogenation of **1a** at all, indicating that the carbonyl ligand on the rhodium atom inhibited the catalysis completely (entry 11).

Carbonyl substituent on the nitrogen atom is necessary for the regioselective hydrogenation. *N*-Acetylindole was also converted into *N*-acetylindoline in 100% GC yield, while the hydrogenation of *N*-methylindole using the Rh(acac)(cod)–2PPh$_3$ catalyst gave a mixture of several compounds.

A variety of substituted indoles were reduced selectively to yield the corresponding indolines by the hydrogenation using Rh(acac)(cod)–2PPh$_3$ catalyst (Table 2). *N*-Boc-indoles **1b**–**d**, bearing a substituent at the 2-position, were hydrogenated smoothly to give **2b**–**d** in high yield (entries 1–3). On the other hand, hydrogenation of *N*-Boc-3-methylindole (**1e**) proceeded sluggishly, and prolongation of the reaction time could not improve the yield of **2e** (entry 4). The hydrogenation of **1f**, which has a 5-methyl substituent, gave **2f** in 91% GC yield but was slower than that of **1b** (entry 5). 5-Methoxy- (**1g**) and methyl indole-5-carboxylate (**1h**) gave **2g** and **2h** in high yield, respectively (entries 6 and 7). The results of entries 5–7 suggest that the reaction rate may be due to the steric effect of the

Table 2. Catalytic hydrogenation of five-membered heteroaromatic compounds[a]

Entry	Substrate	Time/h	Product	Yield/%[b]
1	 **1b**	2	 **2b**	96 (100)
2	 **1c**	12	 **2c**	98
3	 **1d**	3	 **2d**	85
4	 **1e**	2	 **2e**	(7)
5	 **1f**	5	 **2f**	85 (91)
6	 **1g**	3	 **2g**	99 (100)
7	 **1h**	5	 **2h**	95
8[c]	 **1i**	24	 **2i**	84 (92)[d]
9	 **4**	2	 **5**	91 (100)
10	 **6**	2	 **7**	89 (100)
11[e]	 **8**	2	 **9**	65 (98)
12	 **10**	24	 **11**	(17)

[a]The reactions were carried out in 2-propanol at 80 °C under 50 kg/cm^2 of hydrogen unless otherwise noted. Substrate/Rh(acac)(cod)/PPh_3 = 100/1/2. [b]Isolated yields. GC yields are indicated in parentheses. [c]The reaction was carried out at 30 °C. [d]**2a** was generated in 1% GC yield. [e]The reaction was carried out under 20 kg/cm^2 of hydrogen in the presence of Rh(acac)(cod)–DPPF catalyst.

5-substituent rather than its electronic effect. 5-Chloroindole (**1i**) also underwent the selective hydrogenation in the presence of the rhodium catalyst and molecular hydrogen at 30 °C to give **2i** (entry 8). The hydrogenation at 80 °C provided **2a** with hydrodechlorination.

Related five-membered heteroaromatic compounds also underwent the rhodium catalyzed hydrogenation as well. *N*-Protected pyrrole **4** was completely hydrogenated under similar conditions, giving *N-tert*-butoxycarbonylpyrrolidine (**5**) in 91% isolated yield (entry 9). Partial reduction of **4** was not detected by GLC analysis during the hydrogenation. Rh(acac)(cod)–$2PPh_3$ catalyst promoted the hydrogenations of furan **6** and benzofuran **8**, giving **7** and **9**, respectively (entries 10, 11). In the latter case, octahydrobenzofuran was obtained in 38% GC yield, but the reduction of the fused aryl ring was suppressed by use of DPPF instead of triphenylphosphine. The rhodium catalyst enabled hydrogenation of benzothiophene (**10**), but with very low turnover (entry 12). Sulfur compound produced might have deactivated the rhodium catalyst.

In conclusion, the rhodium complex prepared *in situ* from Rh(acac)(cod) and triphenylphosphine, which are commercially available, was effective for catalytic hydrogenation of a wide range of five-membered heteroaromatic compounds. The catalyst may be readily modified by various chiral phosphine ligands. Asymmetric version of the hydrogenation is being developed in our group now.

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7 The hydrogenation of **1a** by Rh(acac)(cod)–$2PPh_3$ was carried out as follows: A mixture of Rh(acac)(cod) (1.6 mg, 5.0 μmol) and triphenylphosphine (2.6 mg, 10.0 μmol) in 2-propanol (1.0 ml) was stirred vigorously at room temperature for 10 min. The resulting mixture was transferred by a cannula to a nitrogen-filled stainless steel autoclave, in which **1a** (109 mg, 0.50 mmol) was placed beforehand. Hydrogen was introduced into the reaction vessel until the pressure gauge indicated 50 kg/cm^2. The reaction mixture was stirred at 80 °C for 2 h. After the solvent was evaporated, the residue was purified by a flash column chromatography on silica gel (hexane/EtOAc = 20/1) to give **2a** (100 mg, 91% yield).

8 The hydrogenation of **1a** proceeded at 10 kg/cm^2 of hydrogen (88% GC yield, for 2 h).

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