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Synthesis of optically active *N*-hydroxylamines by asymmetric hydrogenation of nitrones with iridium catalysts

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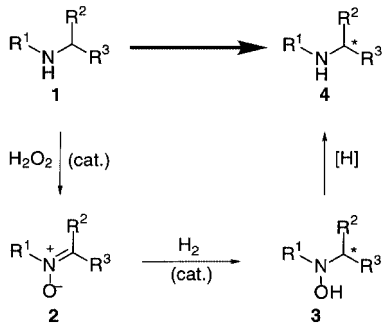
Asymmetric hydrogenation of nitrones with the iridium catalyst system, prepared from $[IrCl(cod)]_2$, (*S*)-BINAP, and $NBu^n_4BH_4$, gives the corresponding *N*-hydroxylamines, which are important as biologically active compounds and precursors of amines, with high enantioselectivity (up to 86% ee).

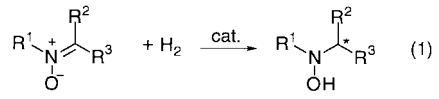
Optically active *N*-hydroxylamines are of interest as biologically active compounds,[1] naturally occurring compounds,[2] and precursors of chiral amino compounds. A catalytic method for synthesis of these compounds is limited to the ruthenium-catalyzed asymmetric hydrosilylation of nitrones.[3] To explore more convenient and economical methods, we pursued the catalytic hydrogenation of nitrones which are obtained readily by catalytic oxidation of secondary amines with hydrogen peroxide.[4] We report herein asymmetric hydrogenation of nitrones with iridium catalysts to give optically active *N*-hydroxylamines. As shown in Scheme 1, catalytic oxidation of amines **1**, followed by catalytic asymmetric hydrogenation of nitrones **2** thus formed provides an efficient and useful route for synthesis of optically active *N*-hydroxylamines **3**. Furthermore, optically active secondary amines **4** can be prepared upon catalytic reduction of **3**.



Scheme 1 Catalytic asymmetric synthesis of chiral amino compounds.

This method is particularly convenient and useful because of the configurational stability of nitrones, ease of handling, and readiness of preparation. Although asymmetric hydrogenation of imines with homogeneous catalysts has been studied extensively,[5] neither asymmetric nor simple hydrogenation of nitrones with homogeneous catalysts are, to our knowledge, known.

We examined the catalytic activity of metal complexes for the hydrogenation of configurationally pure (*E*)-*N*-[1-(4-chlorophenyl)ethylidene]methylamine *N*-oxide **5a**, whose stereochemistry was determined by NOE experiments [eqn. (1)]. When ruthenium complexes were used as catalysts, no hydrogenation occurred. This may be due to the strong affinity of nitrones for ruthernium complexes. Iridium and rhodium complexes, however, showed catalytic activity.



a; R^1=R^3=Me, R^2=4-ClC_6H_4
b; R^1=R^3=Me, R^2=Ph
c; R^1=R^3=Me, R^2=4-BrC_6H_4
d; R^1=R^3=Me, R^2=3-ClC_6H_4
e; R^1=R^3=Me, R^2=2-ClC_6H_4
f; R^1=R^3=Me, R^2=2-naphthyl
g; R^1=$PhCH_2$, R^2=Me, R^3=Ph

Metal complex catalysts bearing the BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] ligand[6] were examined for asymmetric hydrogenation and results are summarized in Table 1. Enantioselectivity was not observed with rhodium catalysts such as $[RhCl(cod)]_2$/(*S*)-BINAP or [Rh{(*S*)-BINAP}(cod)]-ClO_4 (entries 1 and 2). The cationic iridium catalyst, 2.0 mol% [Ir{*R*)-BINAP}(cod)]BF_4 is less reactive, and the enantioselectivity obtained was 27% ee (entry 3). The neutral iridium catalyst, 1.0 mol% $[IrCl(cod)]_2$/(*S*)-BINAP (1.0 : 2.2 mol/mol) gave *N*-hydroxylamine (*R*)-**6a** in 69% yield with 40% ee (entry 4).

These results indicate that iridium catalysts are promising and the ligand coordinated to the iridium plays an important role in the face discrimination of nitrones. A systematic study of neutral iridium catalysts revealed that catalyst systems obtained by treatment of the $[IrCl(cod)]_2$/(*S*)-BINAP complex with hydride sources such as $NBu^n_4BH_4$ or $NaBH_4$ gave higher reactivity and enantioselectivity. The highest enantioselectivity was obtained, when the iridium catalyst system, prepared from 1.0 mol% $[IrCl(cod)]_2$/(*S*)-BINAP/$NBu^n_4BH_4$ (1.0 : 2.2 : 2.0 mol/mol) *in situ*, was used at 0 °C (*R*)-**6a**, 82%, 83% ee, entry 5).† The absolute configuration of **6a** was determined to be *R* by comparison of the optical rotation of the secondary amine derived from **6a** with the reported data.[7] The opposite enantiomer (*S*)-**6a** was obtained, when (*R*)-BINAP was used as a ligand. In this reaction, hydrogen pressure did not affect the enantioselectivity in the range 1–80 kg cm^{-2}. The effect of the solvent on the enantioselectivity is dramatic with THF found to

Table 1 Asymmetric hydrogenation of nitrone **5a** with iridium and rhodium complex catalysts[a]

Entry	Catalyst	Yield[b] (%)	Ee[c] (%)	Configuration
1	$[RhCl(cod)]_2$/(*S*)-BINAP[d]	8[f]	2	—
2	[Rh{(*S*)-BINAP}(cod)]ClO_4[e]	33[f]	0	—
3	[Ir{(*R*)-BINAP}(cod)]BF_4[e]	36	27	(*S*)
4	$[IrCl(cod)]_2$/(*S*)-BINAP[d]	69	40	(*R*)
5	$[IrCl(cod)]_2$/(*S*)-BINAP/$NBu^n_4BH_4$[d]	85 82[g]	73 83[g]	(*R*) (*R*)

[a] Reactions were carried out in the presence of the metal catalyst at 22 °C in THF under hydrogen (80 kg cm^{-2}) for 18 h. [b] Isolated yield. [c] The optical yields were determined by HPLC analysis using a DAICEL CHIRALPAK AD column. [d] 1.0 mol%. [e] 2.0 mol%. [f] Solvent is benzene–methanol (1 : 1). [g] Reaction carried out at 0 °C.

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Table 2 Asymmetric hydrogenation of nitrones with $[IrCl(cod)]_2$/(*S*)-BINAP/$NBu^n_4BH_4$ catalyst system[a]

Entry	Nitrone[b]	Yield[c] (%)	Ee[d] (%)	Configuration[e]
1	**5a**	82	83	(*R*)
2	**5b**	45	69	(*R*)
3	**5c**	76	86	(+)
4	**5d**	68	81	(+)
5	**5e**	17	78	(−)
6	**5f**	64	80	(+)
7[f]	**5g**	78	75	(*R*)

[a] Reactions were carried out in THF at 0 °C under hydrogen (80 kg cm^{-2}) for 18 h in the presence of catalyst. The catalyst was prepared by mixing $[IrCl(cod)]_2$ (1.0 mol%), (*S*)-BINAP (2.2 mol%), and $NBu^n_4BH_4$ (2.0 mol%). [b] Nitrones were configurationally pure. The stereochemistry was determined by NOE experiments. [c] Isolated yield. [d] The optical yields were determined by HPLC analyses using chiral columns. **5a**, **c**–**f**: CHIRALPAK AD, **5b**: CHIRALCEL OD-H, **5g**: CHIRALCEL OJ. [e] See text. [f] Reaction carried out at 22 °C

be best.† Toluene led to moderate enantioselectivity while methanol and dichloromethane gave poor results.

Various nitrones can be hydrogenated enantioselectively with the $[IrCl(cod)]_2$/(*S*)-BINAP/$NBu^n_4BH_4$ catalyst system (Table 2). In the reaction of (*E*)-*N*-1-(arylethylidene)methylamine *N*-oxides, the reactivity and enantioselectivity are increased noticeably by introduction of an electron-withdrawing group on the aryl group. The hydrogenation of nitrones bearing *para*- and *meta*-halogens, **5c** and **5d**, proceeded smoothly to give the corresponding *N*-hydroxylamines with enantioselectivity of 86 and 81% ee, respectively (entries 3 and 4). However, the hydrogenation of *ortho*-chlorinated compound **5e** proceeded slowly (entry 5). The hydrogenation of nitrone **5f** bearing a naphthyl group at the α-position of nitrogen gave the corresponding *N*-hydroxylamine with 80% ee (entry 6). The *N*-benzyl substituted nitrone **5g** was hydrogenated with 75% ee (entry 7). The absolute configurations of **6b**[7] and **6g**[5j] were determined to be *R*.

We prepared $[IrH(\eta^1,\eta^3\text{-}C_8H_{12})\{(S)\text{-BINAP}\}]$ **7** in 59% yield from $[IrCl(cod)]_2$, (*S*)-BINAP and KOH in methanol–benzene (1 : 1). Under the conditions of hydrogenation, the C_8H_{12} group of **7** is reduced to cyclooctane, and complex **7** would be converted to $[IrH\{(S)\text{-BINAP}\}(THF)_n]$. Using complex **7** as a catalyst for the hydrogenation of **5a** led to *N*-hydroxylamine **6a** with 86% ee (*R*). This result is comparable to the 83% ee (*R*) obtained with the $[IrCl(cod)]_2$/(*S*)-BINAP/$NBu^n_4BH_4$ catalyst system above, indicating that iridium–hydride species appear to form from $[IrCl(cod)]_2$/(*S*)-BINAP/$NBu^n_4BH_4$ mixtures and lead to high enantioselectivity for asymmetric hydrogenation of nitrones.

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Notes and references

† *Typical experimental procedure*: a Schlenk flask was charged with $[Ir(cod)Cl]_2$ (3.4 mg, 0.0050 mmol), (*S*)-BINAP (6.8 mg, 0.011 mmol), $NBu^n_4BH_4$ (2.6 mg, 0.010 mmol) and degassed THF (2.5 mL) under argon atmosphere and the mixture stirred for 15 min at room temperature. The solution of the catalyst was transferred to an autoclave, and (*E*)-*N*-[1-(4-chlorophenyl)ethylidene]methylamine *N*-oxide **5a** (92.2 mg, 0.50 mmol) added under argon. The argon gas in the autoclave was replaced by hydrogen in three cycles (20 kg cm^{-2}) and finally pressurized with hydrogen to 80 kg cm^{-2}. The mixture was stirred at 0 °C for 18 h. After the autoclave was vented and opened, the reaction mixture was transferred to a flask. The solvent was evaporated under reduced pressure. The product was purified by SiO_2 column chromatography (**6a**; 76.1 mg, 0.41 mmol, 82% yield). The enantiomeric excess was determined to be 83% by HPLC using a DAICEL CHIRALPAK AD. Optically pure *N*-hydroxylamine **6a** was obtained by recrystallization from acetone {**6a**, mp 97.5–98 °C, $[\alpha]_D$ +50.0 (c = 1.00, EtOH)}. The corresponding optically pure secondary amine was obtained by treatment of optically pure **6a** with molecular hydrogen over a palladium catalyst or by treatment with zinc/HCl.

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