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Regio- and chemoselective transfer hydrogenation of quinolines catalyzed by a Cp*Ir complex

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Abstract—An efficient method for the transfer hydrogenation of quinolines catalyzed by a Cp*Ir complex was developed. A variety of 1,2,3,4-tetrahydroquinolines were obtained by regio- and chemoselective transfer hydrogenation of quinolines using 2-propanol as a hydrogen source.

1,2,3,4-Tetrahydroquinoline derivatives have attracted considerable attention owing to their importance as synthetic intermediates for drugs, agrochemicals, and dyes.[1] Among a number of methods for the synthesis of 1,2,3,4-tetrahydroquinolines, the regioselective reduction of quinolines[2,3] might be the simplest and most promising way because a variety of quinolines can be easily available. Transition metal-catalyzed homogeneous or heterogeneous hydrogenation using molecular hydrogen is the most frequently employed method for reducing the heterocyclic ring in quinolines.[2]

On the other hand, transfer hydrogenation using hydrogen donors has advantages in comparison with the hydrogenation using molecular hydrogen; transfer hydrogenation can be performed under safe and mild conditions in many cases, and this method has been applied to the reduction of unsaturated bonds in wide variety of organic molecules.[4] In spite of recent progress in the chemistry of transfer hydrogenation, the reaction of nitrogen heteroaromatic compounds has been hardly reported.[5] During the course of our investigation on the chemistry of pentamethylcyclopentadienyl (Cp*) iridium complexes, we found a catalytic activity of $[Cp^*IrCl_2]_2$ toward hydrogen transfer reactions between organic molecules.[6,7] We report here Cp*Ir-catalyzed regio- and chemoselective transfer hydrogenation of quinoline derivatives using 2-propanol as a hydrogen donor.

First, we investigated Cp*Ir-catalyzed transfer hydrogenation of quinoline under various conditions. The results are summarized in Table 1.[8] When a solution of quinoline and catalytic amounts of $[Cp^*IrCl_2]_2$ (1.0 mol%Ir) in 2-propanol (10 mL) was stirred under reflux for 17 h, 1,2,3,4-tetrahydroquinoline was formed in 45% yield (entry 1).[9] The reaction was highly regioselective; other products, such as 1,2-dihydroquinoline, 5,6,7,8-tetrahydroquinoline, or decahydroquinoline were not detected. Addition of base (K_2CO_3 or Et_3N), which effectively accelerated the oxidative hydrogen transfer reactions catalyzed by $[Cp^*IrCl_2]_2$,[6] completely inhibited the present reaction (entries 2 and 3). On the contrary, addition of acid (CF_3CO_2H or $HClO_4$) considerably accelerated the reaction (entries 4 and 5). When 10 mol% of $HClO_4$ was added to the catalytic system, 1,2,3,4-tetrahydroquinoline was obtained in 69% yield accompanied by *N*-isopropyl-1,2,3,4-tetrahydroquinoline (ca. 25%) as a byproduct (entry 5).[10] Formation of this byproduct was suppressed by addition of 0.5 mL of H_2O, and the yield was improved up to 93% (entry 6). Other hydrogen donating solvents (methanol and ethanol) were also examined, however, the yield was lower than in the case of 2-propanol (entries 8 and 9).

We next tried the transfer hydrogenation of a series of quinolines. Results are summarized in Table 2.[8] Reactions of quinolines bearing a methyl group at 2-, 3-, 6-, 7-, and 8-position proceeded successfully to give the

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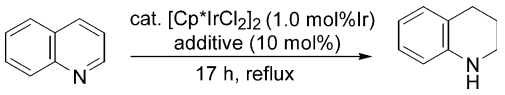
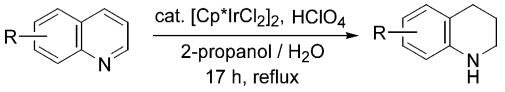
Table 1. Cp*Ir-catalyzed transfer hydrogenation of quinoline under various conditions[a]



Entry	Solvent	Additive	Yield (%)[b]
1	2-Propanol (10 mL)	None	45
2	2-Propanol (10 mL)	K_2CO_3	0
3	2-Propanol (10 mL)	Et_3N	0
4	2-Propanol (10 mL)	CF_3CO_2H	75
5	2-Propanol (10 mL)	$HClO_4$[c]	69[d]
6	2-Propanol (9.5 mL) + H_2O (0.5 mL)	$HClO_4$[c]	93
7	2-Propanol (9.5 mL) + H_2O (0.5 mL)	None	76
8	Methanol (10 mL)	None	0
9	Ethanol (10 mL)	None	0[e]

[a] The reaction was carried out with quinoline (2.0 mmol), $[Cp^*IrCl_2]_2$ (1.0 mol%Ir), and additive (0.20 mmol) in solvent (10 mL) under reflux for 17 h.
[b] Determined by GC.
[c] 60% $HClO_4$ aq was used.
[d] *N*-Isopropyl-1,2,3,4-tetrahydroquinoline was formed as byproduct.
[e] *N*-Ethyl-1,2,3,4-tetrahydroquinoline was formed (34%).

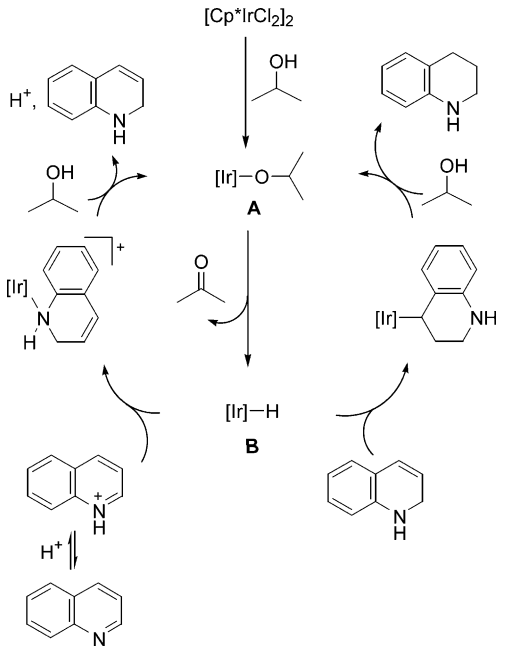
Table 2. Cp*Ir-catalyzed transfer hydrogenation of substituted quinolines[a]



Entry	R	Cat. (mol%Ir)	$HClO_4$ (mol%)	Yield (%)[b]
1	H	1.0	10	(93)
2	H	2.0	0	89
3	2-Me	4.0	0	82
4	3-Me	2.0	10	79
5	4-Me	4.0	0	39
6	6-Me	2.0	10	78[c]
7	7-Me	2.0	10	78[c]
8[d]	8-Me	2.0	10	82
9[e]	5-NO_2	4.0	10	72
10	6-NO_2	2.0	0	94
11	6-Cl	2.0	10	78[c]
12	6-Br	2.0	10	70[c]
13	6-CO_2H	4.0	10	64
14	6-OMe	1.9	11	79[c]

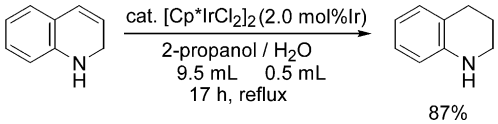
[a] The reaction was carried out with quinolines (2.0 mmol), $[Cp^*IrCl_2]_2$, and 60% $HClO_4$ aq in solvent (2-propanol 9.5 mL + H_2O 0.5 mL) under reflux for 17 h.
[b] Isolated yield. The values in parentheses are GC yield.
[c] Small amount of *N*-isopropyl-1,2,3,4-tetrahydroquinoline derivative was formed as byproduct (5–10%).
[d] Reaction time was 24 h.
[e] Reaction time was 64 h.

corresponding 1,2,3,4-tetrahydroquinolines in good yields (entries 3, 4, and 6–8).[11] Reactions of quinolines bearing electron-withdrawing (NO_2, Cl, Br, and CO_2H) and electron-donating (OMe) substituent proceeded chemoselectively in good to excellent yields (entries 9–14). It should be noted that nitro group was tolerant in the present catalytic system. The present transfer hydrogenation system was highly effective for quinolines, however, hydrogenation of isoquinolines or pyridines was so far unsuccessful.



Scheme 1.

A possible mechanism would be as follows (Scheme 1): The first step of the reaction would involve formation of iridium isopropoxide **A** by the reaction of catalyst precursor $[Cp^*IrCl_2]_2$ with 2-propanol. Then β-elimination would occur to afford iridium hydride **B**. The carbon–nitrogen double bond of quinolinium ion generated by the protonation of quinoline would insert into iridium–hydride bond in **B** to afford 1,2-dihydroquinoline intermediate. The carbon–carbon double bond of 1,2-dihydroquinoline would insert into iridium–hydride bond in **B** followed by protonolysis to give 1,2,3,4-tetrahydroquinoline product. Although 1,2-dihydroquinoline intermediate could not be detected in the course of reaction, the similar reaction of 1,2-dihydroquinoline as above (without addition of $HClO_4$) gave 1,2,3,4-tetrahydroquinoline in high yield (Eq. 1), supporting the presented mechanism.



(1)

In summary, we have developed a new system for transfer hydrogenation of quinolines catalyzed by a Cp*Ir complex using 2-propanol as a hydrogen source to afford 1,2,3,4-tetrahydroquinolines in regio- and chemoselective manner.

Acknowledgements

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8. Typical procedure: In a 50 mL glass reactor under an atmosphere of argon were placed $[Cp^*IrCl_2]_2$ in 2-propanol (9.5 mL) and H_2O (0.5 mL). Then quinolines (2.0 mmol) and 60% $HClO_4$ aq (10 mol %) were added, and the mixture was stirred under reflux for 17 h. GC yields were obtained by using undecane as an internal standard (Shimadzu GC-14A gas chromatograph with capillary column CBP1-M25-025). The products were isolated by silica gel column chromatography. The products were identified by NMR analysis.
9. $[Cp^*IrHCl]_2$ also showed catalytic activity to give 1,2,3,4-tetrahydroquinoline in 34% yield, while other catalysts such as $[Cp^*IrCl(PPh_3)_2]CF_3SO_3$, $[IrCl(cyclooctene)_2]_2$ or $IrCl_3{\cdot}5H_2O$ did not show any activity.
10. *N*-Isopropyl-1,2,3,4-tetrahydroquinoline would be formed via N-alkylation of 1,2,3,4-tetrahydroquinoline. Cp^*Ir-catalyzed N-alkylation of amines with alcohols has been reported by us.[6c]
11. Reaction of 4-methylquinoline was sluggish; the yield was 39% even with higher catalyst loading and longer reaction time (Table 2, entry 5). Addition of $HClO_4$ was not effective for this reaction.