**CHINESE JOURNAL OF CATALYSIS**
Volume 28, Issue 10, October 2007
Online English edition of the Chinese language journal

Available online at www.sciencedirect.com
ScienceDirect

**Cite this article as:** Chin J Catal, 2007, 28(10): 847–849.

SHORT COMMUNICATION

# Iridium-Catalyzed Asymmetric Hydrogenation of (2*H*-chromen-3-yl)methanols

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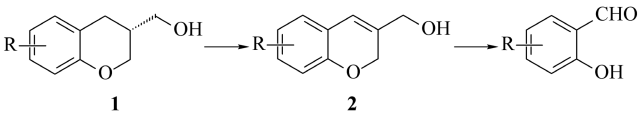
**Abstract:** *Trans*-cyclohexane-backbone iridium complexes with different axial chirality were synthesized from (1*R*,2*S*)-2-(pyridin-2-yl) cyclohexanol, and their application in asymmetric hydrogenation of (2*H*-chromen-3-yl)methanols was investigated. When the hydrogenation was carried out using 1% **Ir-8** as the catalyst at a hydrogen pressure of 5 MPa in dichloromethane for 16 h at room temperature, excellent activities and up to 94% ee were obtained.

**Key Words:** (2*H*-chromen-3-yl)methanol; asymmetric hydrogenation; iridium catalyst

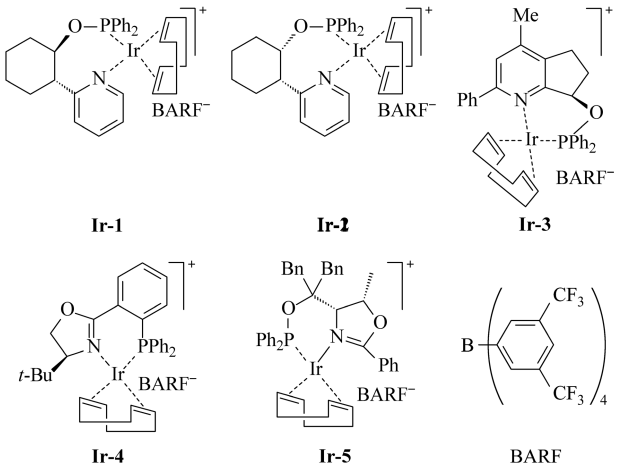
The importance of the chromane skeleton in the area of biologically active compounds is well recognized. For example, 3-hydroxymethylchromanes are important intermediates in the synthesis of $\alpha$-adrenergic blocking agents and nootropic drugs [1]. However, the preparation of optically active 3-hydroxymethylchromanes was reported in only a few examples. In 1996, Zecchi's group [2] used a molecular [3+2] cycloaddition strategy to get a series of chiral 3-hydroxymethylchromanes. Subsequently, in 2003, Hanselmann's group [3] developed Lewis acid-catalyzed [3+2] cycloaddition to synthesize 3-hydroxymethylchromane.

Through a retrosynthetic analysis (Scheme 1), the simplest method to prepare chiral 3-hydroxymethylchromanes (**1**) is the asymmetric hydrogenation of (2*H*-chromen-3-yl)methanols (**2**). As an extension of our work on the asymmetric hydrogenation of unfunctionalized olefins [4,5], we report here a method to synthesize chiral 3-hydroxymethylchromanes by iridium-catalyzed asymmetric hydrogenation [6].




**Scheme 1** The retrosynthetic analysis of 3-hydroxymethylchromanes

(2*H*-chromen-3-yl)methanols can be conveniently synthesized from substituted salicylaldehydes according to a method in the literature [7]. Using (2*H*-chromen-3-yl)methanol as a model substance, we evaluated five different classes of iridium complex catalysts (Scheme 2): cyclohexane-backbone **Ir-1** and **Ir-2** [4] and biocyclic **Ir-3** [5] developed by us, and PHOX (phosphinooxazoline)-derivatized **Ir-4** [8] and Thre-PHOX-derivatized **Ir-5** [9] developed by Pfaltz's group.




**Scheme 2** Iridium complexes used in asymmetric hydrogenation of (2*H*-chromen-3-yl)methanol

**Received date:** 2007-06-19.

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**Foundation item:** Supported by the National Natural Science Foundation of China (20672112).

The hydrogenation was carried out using 1% (molar fraction) catalyst and a hydrogen pressure of 5 MPa in dichloromethane. As shown in Table 1, only **Ir-1**, **Ir-2**, and **Ir-4** gave full conversion at room temperature after 16 h, and **Ir-1** was the most promising catalyst. In comparison to **Ir-1**, **Ir-2** showed a slightly lower enantioselectivity (75% ee in entry 2 vs 81% ee in entry 1). However, the enantioselectivity of the product using catalyst **Ir-4** was much lower and only 51% ee was obtained (entry 4). Very unfortunately, the low activity catalysts **Ir-3** and **Ir-5** gave poor enantioselectivities (52% ee in entry 3 and 34% ee in entry 5). After a careful comparison, the cyclohexane-backbone **Ir-1** series was chosen to further improve the enantioselectivity of the reaction.

**Table 1** Iridium-catalyzed asymmetric hydrogenation of (2*H*-chromen-3-yl)methanol

**2a** **1a**

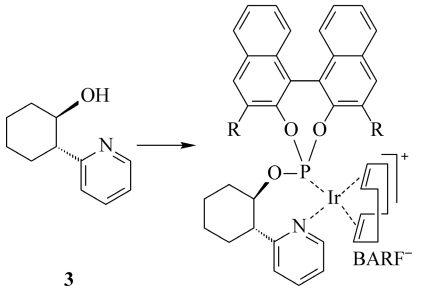
| Entry | Complex | Conversion [a] (%) | ee [b] (%) |
|---|---|---|---|
| 1 | **Ir-1** | >99 | 81 (*R*) |
| 2 | **Ir-2** | >99 | 75 (*R*) |
| 3 | **Ir-3** | 20 | 52 (*R*) |
| 4 | **Ir-4** | >99 | 51 (*S*) |
| 5 | **Ir-5** | 60 | 34 (*R*) |
| 6 | **Ir-6** | >99 | 89 (*R*) |
| 7 | **Ir-7** | >99 | 90 (*R*) |
| 8 | **Ir-8** | >99 | 94 (*R*) |

Reaction conditions: substrate 0.25 mmol, complex 0.0025 mmol, dichloromethane 2 ml, hydrogen pressure 5 MPa, room temperature, 16 h.

[a] Determined by $^1$H NMR.

[b] Determined by chiral HPLC (OJ-H).

Considering the accessibility of materials, we decided to alter the substituting group of the phosphorus atom in the catalyst from diphenyl to the BINOL (1,1'-bi-2-naphthol) derivative. Following the literature procedure [4], enantiopure (1*R*,2*S*)-**3** was deprotonated with *n*-BuLi and then treated with BINOL-derivatized chlorophosphine to afford the desired *N*,*P*-ligands after column separation. Subsequently, these ligands were reacted with $[Ir(COD)Cl]_2$ and then exchanged with NaBARF (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate sodium) to afford iridium complex catalysts **Ir-6** and **Ir-7** (Scheme 3). Very interestingly, both (*R*)- and (*S*)-BINOL-phosphite derivatized catalysts gave full conversion and similar enantioselectivities (89% ee in entry 6 and 90% ee in entry 7), which were superior to **Ir-1**. These results inspired us to synthesize a more sterically hindered BINOL-derivatized catalyst. Therefore, 3,3'-diphenyl-(*S*)-BINOL-phosphite was linked to obtain catalyst **Ir-8** (Scheme 3). To our delight, catalyst **Ir-8** also gave full conversion and a higher enantioselectivity (94% ee in entry 8).



**3**

**Ir-6**: 1*R*, 2*S*, *Ra*, R = H
**Ir-7**: 1*R*, 2*S*, *Sa*, R = H
**Ir-8**: 1*R*, 2*S*, *Sa*, R = Ph

**Scheme 3** Synthetic procedure for the iridium complex catalysts (The synthesis conditions are the same as in Ref. [4].)

Under the above optimized conditions, the enantioselective hydrogenation of substituted (2*H*-chromen-3-yl)methanols **2a–2h** was evaluated using catalyst **Ir-8** (Table 2). When the OMe group was changed from the 7- to 6- or 8-position, full conversion was obtained except for the 8-substituted compound (98% conversion in entry 2). However, the ee value of the products decreased from 94% to 87% or 88%, respectively. Next, different 6-position substituted groups were studied to investigate their effects on activity and enantioselectivity. It was found that when the 6-position substituted group was an alkyl, full conversion was obtained (entries 5 and 6). Among these, the substances with the methyl and more sterically hindered *t*-Bu group gave 90% ee (entry 5) and higher 94% ee (entry 6), respectively. When the 6-position substituted group was phenyl, full conversion and lower enantioselectivity were obtained (85% ee in entry 7). For the *β*-naphthyl-1-formaldehyde-derivatized substance (**2h**), catalyst **Ir-8** gave full conversion and 92% ee (entry 8).

**Table 2** **Ir-8**-catalyzed asymmetric hydrogenation of (2*H*-chromen-3-yl)methanols

**2a−2h** **1a−1h**

| Entry | Substrate | R | Conversion (%) | ee (%) |
|---|---|---|---|---|
| 1 | **2a** | H | >99 | 94 (*R*) |
| 2 | **2b** | 8-OMe | 98 | 88 (*R*) |
| 3 | **2c** | 7-OMe | >99 | 94 (*R*) |
| 4 | **2d** | 6-OMe | >99 | 87 (*R*) |
| 5 | **2e** | 6-Me | >99 | 90 (*R*) |
| 6 | **2f** | 6-*t*-Bu | >99 | 94 (*R*) |
| 7 | **2g** | 6-Ph | >99 | 85 (*R*) |
| 8 | **2h** | 5,6 = –(CH=CH)$_2$– | >99 | 92 (*R*) |

Reaction conditions are the same as in Table 1.

In summary, iridium-catalyzed asymmetric hydrogenation of (2*H*-chromen-3-yl)methanols to chiral 3-hydroxymethylchromanes was performed and catalyst **Ir-8** showed excellent activity and up to 94% ee.

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