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Kana Sakamoto and Takahiro Nishimura*

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Abstract. Catalytic asymmetric hydroarylation of 2H-chromenes with aromatic ketones was realized by use of a cationic iridium/chiral phosphine complex. The reaction proceeded via olefin isomerization, followed by enantioselective hydroarylation, thus giving 2-arylchromanes in high yields with high enantioselectivity.

Keywords: Iridium; C–H activation; Chromanes; Ketones; Asymmetric synthesis

The chromane (benzodihydropyran) skeleton is a privileged scaffold found in natural products and drug candidates representing bioactivities such as antioxidant, antitumor, and antibacterial properties.[1]

Of the chromane derivatives, flavans, which include a 2-phenyl-3,4-dihydro-2H-chromene skeleton, are widely distributed in plants and also exhibit a wide variety of bioactivities. In order to investigate their pharmacological properties, the asymmetric synthesis of 2-arylchromanes has been developed. There have been several reports on the asymmetric synthesis of flavans[3] a) cyclization of chiral haloalkyl ortho-bromophenyl ethers via C–C bond formation,[3] b) intramolecular C–O bond formation of chiral alcohols,[4] c) ring-closing metathesis of chiral alkenyl ortho-vinylphenyl ether followed by hydrogenation,[5] d) cyclization of chiral epoxides,[6] e) enantioselective intramolecular oxysulfenylation and oxa-oxyselenenylation of ortho-alkenylphenols,[7] and f) enantioselective hydrogenation of 2-aryl-4H-chromenes.[8]

Recently, we reported the regio- and enantioselective hydroarylation of alkyl ethers catalyzed by an Ir/chiral bisphosphine complex.[9a] The reaction involves directed ortho–C–H activation of aromatic compounds such as 2-phenylpyridine derivatives and the regioselective hydroarylation of 1-alkenyl ethers isomerized from alkyl ethers such as allyl and homoallyl ethers. Consequently, the aryl groups are selectively installed at the α-carbon atom of the alkoxy group. Based on our previous studies, we focused on the enantioselective synthesis of a variety of 2-arylcromane derivatives.[10] Here we report iridium-catalyzed enantioselective hydroarylation[11,12] of readily available 2H-chromenes[13] with aromatic ketones involving olefin isomerization (Scheme 1). The reaction gave 2-arylchromanes in high yields with high enantioselectivity.

![Scheme 1. Ir-Catalyzed Asymmetric Hydroarylation of Chromenes.](image)

Treatment of p-methoxyacetophenone (1a) with 1.5 equivalents of 2H-chromene (2a) in the presence of [IrCl(cod)]$_2$ (5 mol% of Ir), (R)-binap[14] (6 mol%), and NaBAR$_4$ (10 mol%, Ar$^r$ = 3,5-(CF$_3$)$_2$C$_6$H$_3$) in toluene at 80 ºC for 18 h gave the addition product 3aa in 88% yield with 84% ee (Table 1, entry 1). The aryl group was selectively installed into the 2-position of the chromene core. Higher enantioselectivity (89% ee) was obtained with a bulkier ligand, (R)-DM-binap (entry 2), while the use of (R)-Tol-binap was less effective in terms of both the reactivity and enantioselectivity (entry 3). (R)-Binap*[15] having 3,5-dimethyl-4-methoxy groups on the phosphorous atom showed a nearly identical enantioselectivity to that obtained with (R)-DM-binap (entry 4). (S)-Segphos[16] showed similar reactivity to binap (entry 5) and the use of the bulkier ligand, (R)-DM-segphos, improved the enantioselectivity to 89% ee (entry 6). However, the use of a much bulkier ligand (R)-DTBM-segphos gave no addition product.

UPDATE

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**Iridium-Catalyzed Asymmetric Hydroarylation of Chromene Derivatives with Aromatic Ketones: Enantioselective Synthesis of 2-Arylchromanes**

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acetophenones proceeded enantioselectively to give DM with a chiral stationary phase column: Chiralcel OD Determined by (10 mol%) in toluene (0.2 mL) at 80 ºC for 18 h. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield [%][b]</th>
<th>ee [%][c]</th>
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<tr>
<td>1</td>
<td>(R)-binap</td>
<td>88</td>
<td>84</td>
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<tr>
<td>2</td>
<td>(R)-DM-binap</td>
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<td>89</td>
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<td>(R)-Tol-binap</td>
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<tr>
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</tr>
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<td>-</td>
</tr>
<tr>
<td>12</td>
<td>(R,R)-QuinoxP*</td>
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<td>-</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>0</td>
<td>-</td>
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[b] Reaction conditions: 1a (0.10 mmol), 2a (0.15 mmol), [IrCl(cod)]2 (5 mol% of Ir), ligand (6 mol%), and NaBARf (10 mol%) in toluene (0.2 mL) at 80 ºC for 18 h. [c] Determined by 'H NMR. [i] Determined by HPLC analysis with a chiral stationary phase column: Chiralcel OD-H.

Scheme 2 summarizes the results obtained for the hydroarylation of 2H-Chromene. Reaction conditions: 1 (0.20 mmol), 2a (0.30 mmol), [IrCl(cod)]2 (5 mol% of Ir), (R)-DM-segphos (6 mol%), and NaBARf (10 mol%) in toluene (0.4 mL) at 80 ºC for 48 h.

This iridium-catalyzed reaction can also be applied to several substituted chromene derivatives (Scheme 3). Thus, chromene derivatives substituted with electron-withdrawing (F, Cl, Br) and -donating...
groups (Me, MeO) (2h–g) are all good substrates to give the corresponding products in good yield with high enantioselectivity. It should be noted that in all cases the aryl groups were selectively installed into the 2-position of the chromane derivatives. Benzo-1,4-dioxene 2h also underwent the hydroarylation with 1a to give the addition product 3ah in 89% yield with 70% ee.

\[
\begin{align*}
1a + [IrCl(cod)]_2 (5 \text{ mol}\% \text{ Ir}) + (R)-\text{DM-sephos} (6 \text{ mol}\%) + \text{NaBAr}_4 (10 \text{ mol}\%) \\
to \quad \text{toluene, } 80^\circ \text{C, } 48 \text{ h}
\end{align*}
\]

\[
\begin{align*}
X = \text{F (3ab)} & \quad 85\%, 84\% \text{ ee} \\
\text{Cl (3ac)} & \quad 73\%, 88\% \text{ ee} \\
\text{OMe (3ad)} & \quad 70\%, 84\% \text{ ee}
\end{align*}
\]

\[
\begin{align*}
X = \text{F (3af)} & \quad 97\%, 92\% \text{ ee} \\
\text{Me (3ag)} & \quad 98\%, 98\% \text{ ee}
\end{align*}
\]

**Scheme 3.** Ir-Catalyzed Asymmetric Hydroarylation of Chromones.

The absolute configuration of the products was assigned by analogy with (S)-3pa, which was transformed into the known chiral flavan (Scheme 4). Thus, treatment of chromone 3pa, which was obtained by using (R)-DM-sephos, with NaOCl solution (8 equiv.) and 1 N NaOHaq (6.2 equiv.) in 1,4-dioxane at 75 °C for 12 h gave 4 in 94% yield. Carboxylic acid 4 was converted into the corresponding aldehyde, which was then subjected to deumplification through an Ir catalysis to give flavan 5. The absolute configuration of 5 was determined to be S-(-) by its specific rotation \([\alpha]_D^{25} = -12 (c = 0.60, \text{CHCl}_3)\) for 79% ee (S); lit. \([\alpha]_D^{20} = -10.6 (c = 0.06, \text{CHCl}_3)\) for (S)-[5].

\[
\begin{align*}
1p + 2a & \quad (0.50 \text{ mmol}) \\
\text{toluene, } 80^\circ \text{C, } 48 \text{ h}
\end{align*}
\]

\[
\begin{align*}
[\text{IrCl(cod)}]_2 (5 \text{ mol}\% \text{ Ir}) + (R)-\text{DM-sephos} (6 \text{ mol}\%) + \text{NaBAr}_4 (10 \text{ mol}\%) \\
toluen, 80^\circ \text{C, } 48 \text{ h}
\end{align*}
\]

\[
\begin{align*}
3p & \quad 79\%, 84\% \text{ ee} \\
4 & \quad 94\% \\
5 & \quad 35\% (3 \text{ steps}), 79\% \text{ ee (S)}
\end{align*}
\]

**Scheme 4.** Transformation into Flavan.

Six-membered chromone derivatives are good substrates undergoing the addition of the C–H bond of aromatic ketones under the present catalytic conditions. Unfortunately, however, seven-membered 2i and 2j were unreactive with aromatic ketones mainly because of the slow isomerization of the alkene moiety. However, it was found that 2-phenylpyridine (1q) reacted with 2i and 2j to give 2-arylated products 3qi and 3qj, respectively, in modest yields with good enantioselectivity (Scheme 5).

\[
\begin{align*}
1q + & \quad \text{Ir}^{+}(R)-\text{DM-sephos} (5 \text{ mol}\% \text{ Ir}) \\
toluene, 80^\circ \text{C, } 48 \text{ h}
\end{align*}
\]

**Scheme 5.** Asymmetric Hydroarylation of 7 and 8-Membered Cyclic Alkenes.

Deuterium-labeling experiments proved that ortho-C–H activation of 4-methoxycetophene (1a) occurred in the presence of the cationic iridium complex. Thus, in the reaction of 1a with deuterated p-methoxystyrene 6, deuterium was transferred from 6 to ortho-positions of 1a [Eq. (1)]. The result indicates that the C–H activation of 1a giving an aryl(hydrido)iridium and reversible insertion/elimination between the hydrido-iridium and 6 occurred. The result also implies that the isomerization of 2H-chromene 2a into 4H-chromene 2a' is presumably promoted by the aryl(hydrido)iridium. In contrast, as shown in Equation 2, the cationic iridium complex can also isomerize 2H-chromene 2a into 4H-chromene 2a'.

\[
\begin{align*}
1a + D & \quad \text{toluene, } 80^\circ \text{C, } 3 \text{ h}
\end{align*}
\]

**On the basis of the deuterium-labeling experiments and the recent computational studies on the Ir-catalyzed hydroarylation,** the catalytic cycle of the present reaction is proposed as illustrated in Scheme 6. Ortho-C–H activation of a cationic iridium A forms an aryl(hydrido)iridium(I) species B. Species B undergoes irreversible carbometalation to 4H-
chromene 2a’ leading to the alkyliridium intermediate C, and reductive elimination forming a C–H bond gives an addition product and regenerates A. The species B promotes olefin isomerization of 2H-chromene 2 into 4H-chromene 2a’ by reversible alkene insertion via alkyliridium E. The isomerization can also be promoted by the cationic iridium(I) via π-allyl complex F formed by allylic C–H activation.[26]

![Scheme 5. Plausible Catalytic Cycle.](image)

In summary, we have developed asymmetric hydroarylation of 2H-chromenes with aromatic ketones by use of a cationic iridium/chiral phosphine complex. The reaction proceeded via olefin isomerization, followed by enantioselective hydroarylation, thus giving 2-arylcromanes in high yields with high enantioselectivity.

**Experimental Section**

For detailed experimental information and the characterization of compounds, see the supporting information.

**General procedure for Ir-catalyzed asymmetric hydroarylation of 2H-chromene:** [IrCl(cod)]$_2$ (3.4 mg, 0.0050 mmol, 5 mol% of Ir), (R)-DM-segphos (8.7 mg, 0.012 mmol, 6 mol%), NaBAr$_4$$_4$ (18.4 mg calculated as the dihydrate, 0.020 mmol, 10 mol%), and toluene (0.4 mL) were placed in a Schlenk tube under N$_2$, and the mixture was stirred at room temperature for 10 min. Then, aromatic ketone 1 (0.20 mmol) and chromene 2 (0.30 mmol) were added to the tube successively, and the mixture was stirred at 80 °C for 48 h. The mixture was passed through a short column of alumina with CH$_2$Cl$_2$ as an eluent, and the solvent was removed on a rotary evaporator. The residue was subjected to preparative TLC on silica gel eluted with EtOAc/hexane (1:3–1:10) to give 3.

**Acknowledgements**

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**References**


[10] One preliminary result of the asymmetric hydroarylation of 2H-chromene with acetophenone was reported in 9a.


The use of (R)-DM-segphos or (R)-DM-binap resulted in the formation of a low yield of 3fa.

Isomerization of 2j did not proceed at all under the same condition as Scheme 2 using binap as a ligand, regardless of the presence or absence of 1a.
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