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Very Important Publication

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

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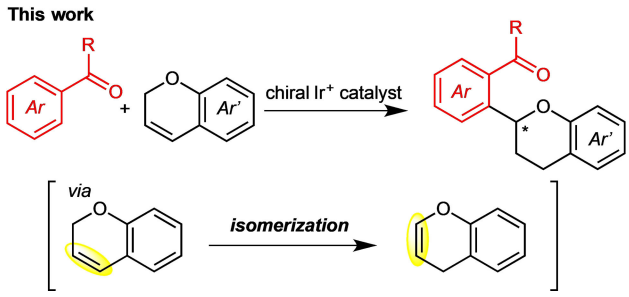
Abstract: Catalytic asymmetric hydroarylation of 2*H*-chromenes with aromatic ketones was realized by use of a cationic iridium/chiral phosphine complex. The reaction proceeded via olefin isomerization, followed by enantioselective hydroarylation, thus giving 2-arylchromanes in high yields with high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

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

The chromane (benzodihydropyran) skeleton is a privileged scaffold found in natural products and drag candidates representing bioactivities such as antioxidant, antitumor, and antibacterial properties.[1] Of the chromane derivatives, flavans, which include a 2-phenyl-3,4-dihydro-2*H*-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;[2] 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 oxyselenenylation of *ortho*-alkenylphenols,[7] and f) enantioselective hydrogenation of 2-aryl-4*H*-chromenes.[8]

Recently, we reported the regio- and enantioselective hydroarylation of alkenyl 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 alkenyl 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-arylchromane derivatives.[10] Here we report iridium-catalyzed enantioselective hydroarylation[11,12] of readily available 2*H*-chromenes[13] with aromatic ketones involving olefin isomerization (Scheme 1). The reaction gave 2-arylchromanes in high yields with high enantioselectivity.



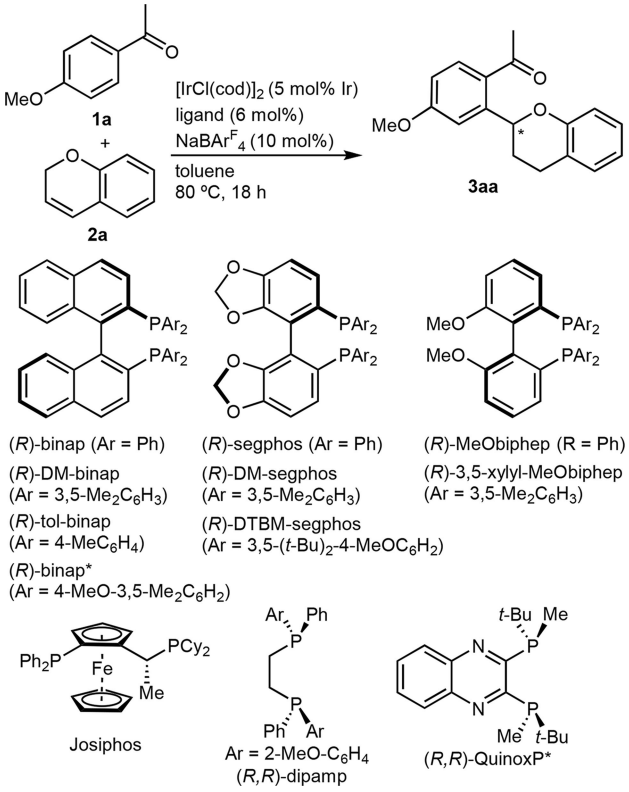
Scheme 1. Ir-Catalyzed Asymmetric Hydroarylation of Chromenes.

Treatment of *p*-methoxyacetophenone (**1a**) with 1.5 equivalents of 2*H*-chromene (**2a**) in the presence of $[IrCl(cod)]_2$ (5 mol% of Ir), (*R*)-binap[14] (6 mol%), and $NaBAr^F_4$ (10 mol%, $Ar^F = 3,5\text{-}(CF_3)_2C_6H_3$) in toluene at 80 °C 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 chromane 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 **3aa** (entry 7). MeObiphep[17] ligands were also effective in inducing the high enantioselectivity (entries 8 and 9). In contrast, the use of Josiphos,[18] dipamp,[19] and QuinoxP*[20] inhibited the reaction (entries 10–12). 1,5-Cyclooctadiene (cod) did not work as a ligand in the present reaction (entry 13).

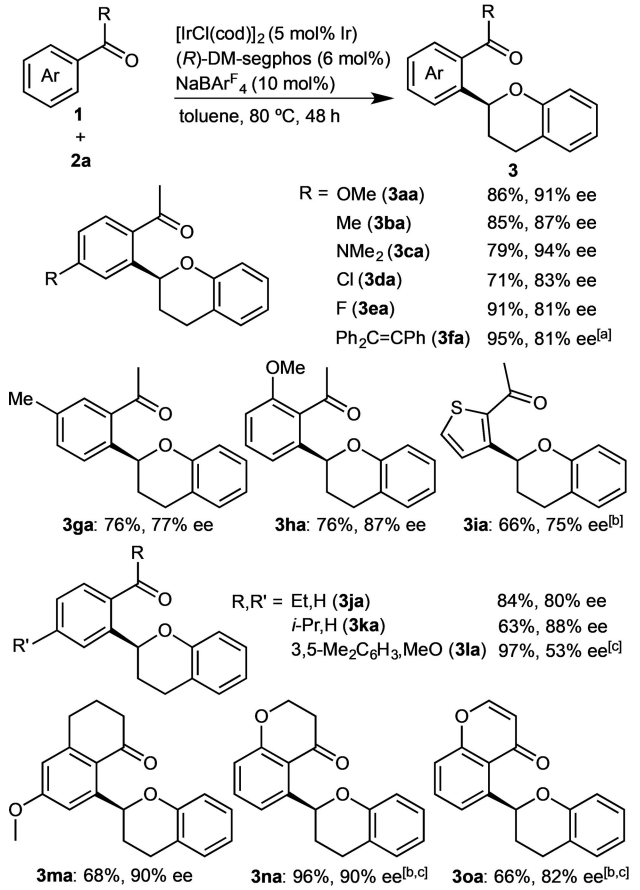
Scheme 2 summarizes the results obtained for the hydroarylation of 2*H*-chromene (**2a**) with several aromatic ketones using the Ir/(*R*)-DM-segphos (or DM-binap) catalyst. The reaction of substituted acetophenones proceeded enantioselectively to give the corresponding 2-arylchromanes **3aa–ha** in good yields. In particular, the reactions of the ketones with electron-donating groups (**1a–c**, **h**) at the *para*- and *ortho*-position showed the high enantioselectivity. A tetraphenylethenyl group, which has aggregation-in-

Table 1. Ligand Screening.[a]



Entry	Ligand	Yield [%][b]	Ee [%][c]
1	(*R*)-binap	88	84
2	(*R*)-DM-binap	86	89
3	(*R*)-Tol-binap	49	68
4	(*R*)-binap*	94	87
5	(*R*)-segphos	94	84
6	(*R*)-DM-segphos	88	89
7	(*R*)-DTBM-segphos	0	–
8	(*R*)-MeObiphep	94	85
9	(*R*)-3,5-Xylyl-MeObiphep	91	88
10	Josiphos	0	–
11	(*R*,*R*)-dipamp	0	–
12	(*R*,*R*)-QuinoxP*	0	–
13	–	0	–

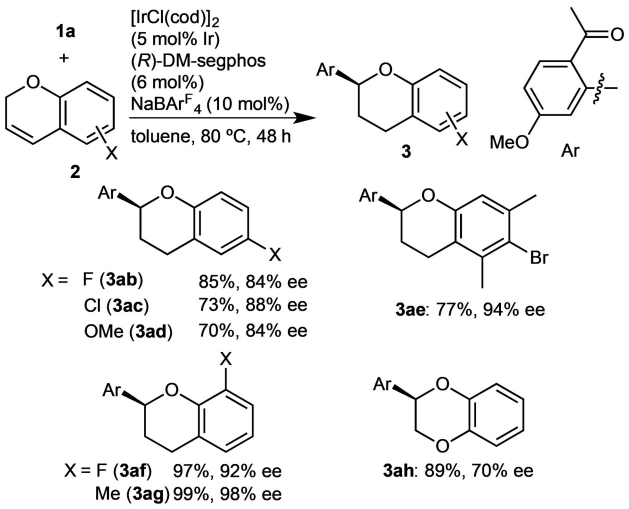
[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), $[IrCl(cod)]_2$ (5 mol% of Ir), ligand (6 mol%), and $NaBAr^F_4$ (10 mol%) in toluene (0.2 mL) at 80 °C for 18 h.
[b] Determined by ^1H NMR.
[c] Determined by HPLC analysis with a chiral stationary phase column: Chiralcel OD-H.



Scheme 2. Ir-Catalyzed Asymmetric Hydroarylation of 2*H*-Chromene. *Reaction conditions*: **1** (0.20 mmol), **2a** (0.30 mmol), $[IrCl(cod)]_2$ (5 mol% of Ir), (*R*)-DM-segphos (6 mol%), and $NaBAr^F_4$ (10 mol%) in toluene (0.4 mL) at 80 °C for 48 h. [a](*R*)-Binap was used instead of (*R*)-DM-segphos. [b]10 mol% of Ir was used. [c](*R*)-DM-Binap was used instead of (*R*)-DM-segphos.

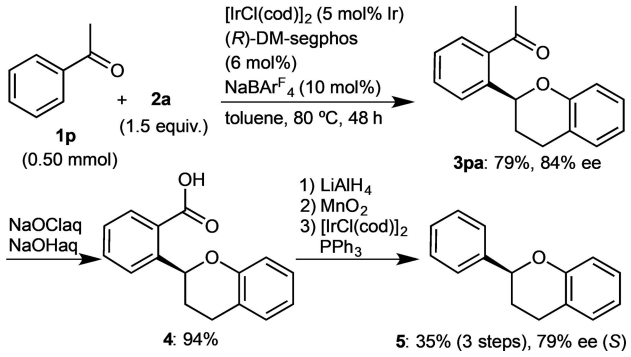
duced emission character,[21] can also be enantioselectively introduced into the chromane skeleton giving **3fa** in 95% yield with 81% ee by using (*R*)-binap.[22] In addition to acetophenones, 2-acetylthiophene (**1i**), ethyl phenyl ketone (**1j**), and isopropyl phenyl ketone (**1k**) were also suitable for this reaction and gave **3ia**, **3ja**, and **3ka**, respectively, with good enantioselectivity. The reaction of substituted benzophenone **1l** also took place using (*R*)-binap to give **3la** in 97% yield, albeit with the modest enantioselectivity (53% ee). Tetralone **1m**, chromanone **1n**, and chromone **1o** also reacted with **2a** to give the corresponding chromanes **3ma–oa** in good yields with high enantioselectivity.

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) (**2b–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.



Scheme 3. Ir-Catalyzed Asymmetric Hydroarylation of Chromenes.

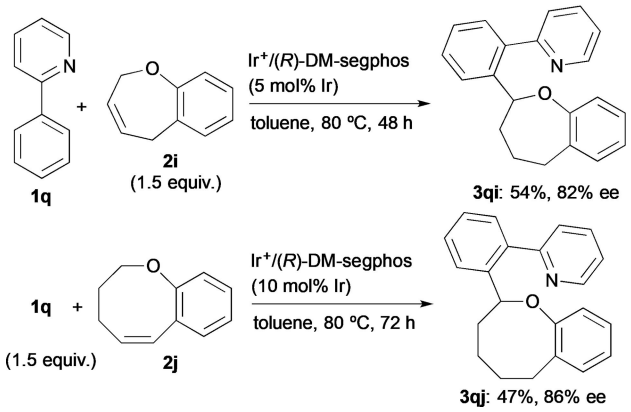
The absolute configuration of the products was assigned by analogy with (*S*)-**3pa**, which was transformed into the known chiral flavan (Scheme 4). Thus, treatment of chromane **3pa**, which was obtained by using (*R*)-DM-segphos, with NaOCl solution (8 equiv.) and 1 N NaOHaq (6.2 equiv.) in 1,4-dioxane 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 deformylation 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, $CHCl_3$) for 79% ee (*S*); lit. $[\alpha]_D^{20}$ −10.6 (c = 0.06, $CHCl_3$) for (*S*)-**5**].[3c]



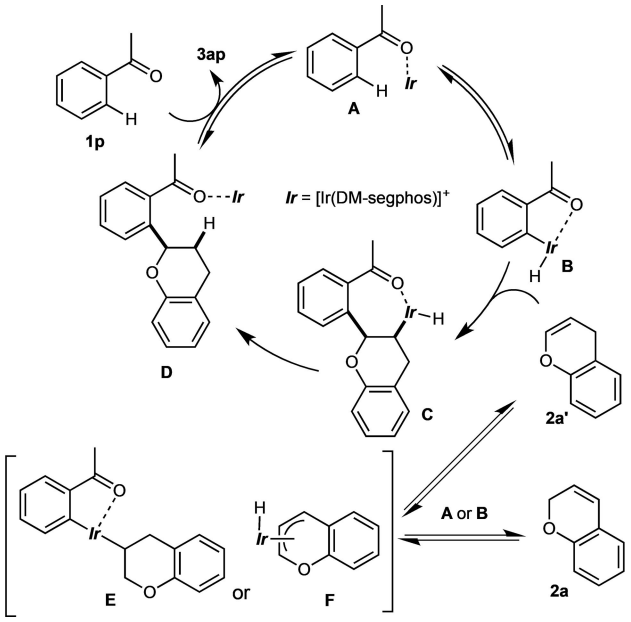
Scheme 4. Transformation into Flavan.

Six-membered chromene derivatives are good substrates undergoing the addition of the C–H bond of aromatic ketones under the present catalytic conditions. Unfortunately, however, seven- and eight-membered **2i** and **2j** were unreactive with aromatic ketones mainly because of the slow isomerization of the alkene moiety.[23] Nevertheless, 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).

Deuterium-labeling experiments proved that *ortho*-C–H activation of 4-methoxyacetophenone (**1a**) occurred in the presence of the cationic iridium complex.[24] Thus, in the reaction of **1a** with deuterated *p*-methoxystyrene **6**,[25] 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 hydridoiridium and **6** occurred. The result also implies that the isomerization of 2*H*-chromene **2a**

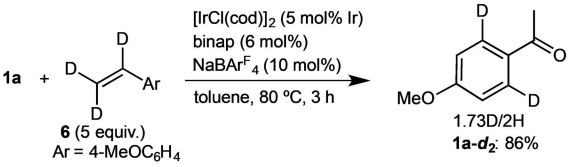


Scheme 5. Asymmetric Hydroarylation of 7 and 8-Membered Cyclic Alkenes.

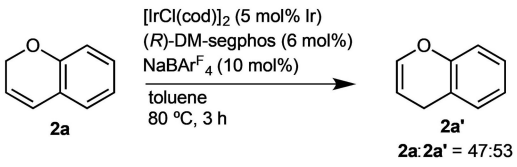


Scheme 6. Plausible Catalytic Cycle.

into 4*H*-chromene **2a**′ is presumably promoted by the aryl(hydrido)iridium. In contrast, as shown in Equation 2, the cationic iridium complex can also isomerize 2*H*-chromene **2a** into 4*H*-chromene **2a**′.[26]



(1)



(2)

On the basis of the deuterium-labeling experiments and the recent computational studies on the Ir-catalyzed hydroarylation,[27] 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 4*H*-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 2*H*-chromene **2** into 4*H*-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]

In summary, we have developed asymmetric hydroarylation of 2*H*-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-arylchromanes 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 2*H*-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%), $NaBAr^F_4$ (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_2Cl_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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