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Highly Enantioselective and Efficient Synthesis of Flavanones Including Pinostrobin through the Rhodium-Catalyzed Asymmetric 1,4-Addition

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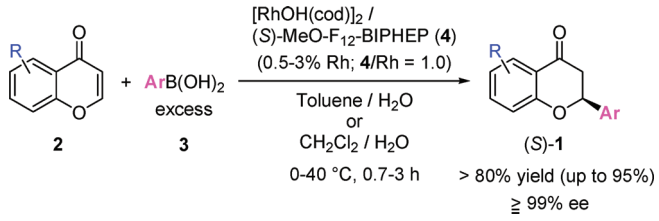
ABSTRACT



An efficient synthesis of bioactive chiral flavanones (1) was achieved through the Rh-catalyzed asymmetric 1,4-addition of arylboronic acid to chromone. The reaction in toluene proceeded smoothly at room temperature in the presence of 0.5% Rh catalyst with electron-poor chiral diphosphine MeO-F_{12}-BIPHEP. In this reaction, the 1,2-addition to (*S*)-1 frequently occurred to yield (2*S*,4*R*)-2,4-diaryl-4-chromanol as a byproduct, which could be reduced by changing the reaction solvent to CH_2Cl_2 to deactivate the Rh catalyst (3% required).

Flavanone (**1a**) and its derivatives (**1**) are found in many natural products that show biological activities[1] such as antioxidant,[2] antitumoral,[3] and antiproliferative properties.[4] However, the optically pure **1** had been prepared by optical resolution of racemic **1** or diastereoselective synthesis from a chiral material, and the efficient synthesis of **1** by asymmetric catalysis had not been known until recently. In 2007, Scheidt et al. reported the catalytic enantioselective synthesis of **1**[5a] through an asymmetric intramolecular oxa-Michael addition and decarboxylation by using a chiral organic[5a,b] or transition-metal catalyst.[5c] Although this method is effective for the synthesis of **1**, the asymmetric induction of an aryl group into commercially available chromone **2a** would be a more convenient and efficient method to synthesize **1**. In particular, the rhodium-catalyzed asymmetric 1,4-addition of arylboronic

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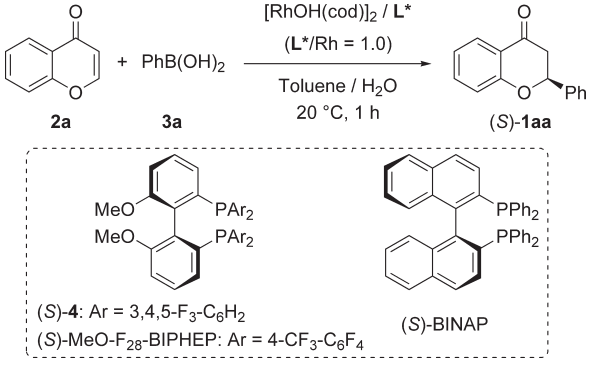
acid (**3**) or that of its derivatives to α,β-unsaturated ketones,[6,7] which have recently been under active investigation,[8] are extremely promising. However, there has been only one report of asymmetric catalysis for the addition of the aryl group into **2**,[9,10] and the catalysis using 5% Rh/chiral bis-sulfoxide required the use of Ar_4BNa instead of **3** and a long reaction time of 24 h to give a moderate yield of **1**. One of the reasons for this insufficient result is due to the less reactive substrate of **2** in the Rh-catalyzed catalysis. Recently, we reported a high-performance Rh catalyst bearing (6,6′-dimethoxybiphenyl-2,2′-diyl)bis[bis-(3,4,5-trifluorophenyl)phosphine] (MeO-F_{12}-BIPHEP, **4**) for the asymmetric 1,4-addition of **3**.[11] The reaction of **3** with an α,β-unsaturated ketone in the presence of Rh/(*R*)-**4** showed a high turnover frequency of up to 53000 h^{-1} in the model reaction[11b] or gave optically pure 4-phenylchroman-2-one in high yield.[11c] In particular, in the latter case, the fact that the Rh/(*R*)-**4** catalyst was highly effective for the less reactive coumarin substrate, which is a structural isomer of **2**, raised our hopes for the success of the reaction of **2**. Therefore, we attempted the efficient synthesis of chiral flavanones by using the Rh/**4** catalyst.

Typically, the Rh-catalyzed asymmetric 1,4-additions have been performed using Rh-Cl species as precatalysts, which are converted to Rh-OH species as an active species by treatment with base such as KOH in situ.[12] However, flavanone **1** undergoes ring-opening under strongly basic conditions.[13] Therefore, we used a $[RhOH(cod)]_2$ complex as a catalyst precursor to avoid basic conditions. Although the use of $[RhOH(cod)]_2$ with chiral ligands for the asymmetric 1,4-addition often decreases the enantioselectivity of the products because of the high catalytic activity of $[RhOH(cod)]_2$ itself,[14] the reaction of **2a** with 2 equiv of phenylboronic acid (**3a**) in the presence of 1.5% $[RhOH(cod)]_2$ complex (3% Rh) in toluene/H_2O at 20 °C for 1 h gave no product (see Table 1, entry 1).[15] The addition of 1 equiv of (*S*)-**4** for Rh largely accelerated the catalysis to yield 60% of (*S*)-flavanone (**1aa**) with 99% ee (entry 2). In this case, no remaining **3a** was observed at the end of the reaction. When 3.5 equiv of **3a** was used, a 95% yield of (*S*)-**1aa** was obtained (entry 3). The catalyst loading could be decreased to 0.5% Rh to yield 93% of (*S*)-**1aa** with 99% ee within just 1 h (entry 4). The effectiveness of the ligand (*S*)-**4** was obvious because the reaction using 3% Rh/(*S*)-MeO-F_{28}-BIPHEP[11a] or Rh/(*S*)-BINAP gave no product under the same conditions (entry 5 or 6).

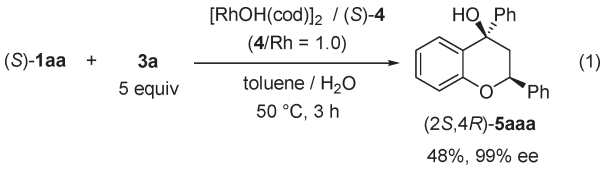
Table 1. Asymmetric 1,4-Addition of **3a** to **2a**



entry	L*	Rh (%)	**3a** (equiv)	**1aa**[a] (%)	ee[b] (%)
1	none	3	2.0	0	
2	(*S*)-**4**	3	2.0	60	99
3	(*S*)-**4**	3	3.5	95	99
4	(*S*)-**4**	0.5	3.5	93	99
5	(*S*)-MeO-F_{28}-BIPHEP	3	2.0	0	
6	(*S*)-BINAP	3	2.0	0	

[a] Isolated yield. [b] The enantiomeric excess was determined by chiral HPLC analyses (see the Supporting Information).

In the case of the reaction using Rh/(*S*)-**4** (entries 3 and 4), 3% of the byproduct 2,4-diphenyl-4-chromanol (**5aaa**),[16] which was the 1,2- and 1,4-adduct,[17] was obtained as a single diastereomer. Because no **5aaa** was observed in the reaction at a 60% conversion (entry 2), the 1,2-addition of the phenyl group proceeded after 1,4-addition. Each phenyl group of **5aaa** was the anti relationship, which was determined by NOE (NOESY) experiment and DFT calculations (see the Supporting Information). Because the stereochemistry of the byproduct **5aaa** was identical to that of the product of the 1,2-addition of **3a** to (*S*)-**1aa** in the presence of 3% Rh/(*R*)-**4** (eq 1), the absolute configuration of the product was (2*S*,4*R*).



Next, we applied 4-tolylboronic acid (**3b**) to the asymmetric 1,4-addition of **2a** (Table 2). In this case, the formation of the byproduct **5abb** severely disturbed the synthesis of (*S*)-**1ab**. The reaction of **2a** with 3.5 equiv of **3b** in the presence of 0.5% $[RhOH(cod)]_2$ complex (1% Rh)

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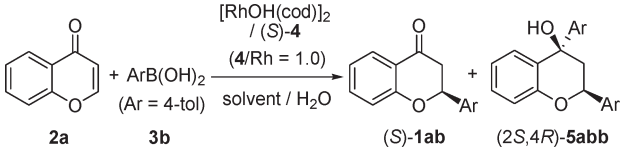
Table 2. Asymmetric 1,4-Addition of **3b** to **2a**



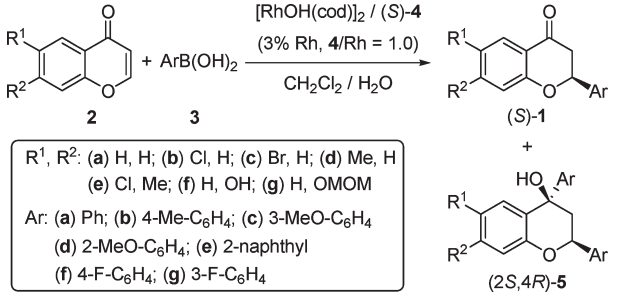
entry	Rh(%)	**3b** (equiv)	solvent	temp (°C)	time (h)	**2a**[a] (%)	**1ab**[a] (%)	**5abb**[a] (%)
1	1	3.5	toluene	20	1	6	59	35
2	1	3.5	toluene	20	0.5	12	66	22
3	1	3.5	toluene	0	1	57	35	8
4	1	2.0	toluene	20	1	37	57	6
5	3	3.5	dioxane	20	1	72	28	0
6	3	3.5	dioxane	20	6	34	51	15
7	3	3.5	$ClCH_2CH_2Cl$	20	1	58	42	<1
8	3	3.5	CH_2Cl_2	20	1	32	67	1
9	3	5.0	CH_2Cl_2	20	1	8	82[b]	10[c]

[a] The ratios were determined by ^{1}H NMR. [b] Isolated yield was 82% with 99% ee. [c] Isolated yield was 7% with 99% ee.

with (*S*)-**4** at 20 °C for 1 h proceeded to yield a 94% conversion, but the ratio of (*S*)-**1ab**/(2*S*,4*R*)-**5abb** was 59:35 (entry 1). At half the reaction time, 22% of (2*S*,4*R*)-**5abb** was observed (entry 2). When the reaction was performed under milder conditions, i.e., a lower temperature or a smaller amount of **3b**, the byproduct (2*S*,4*R*)-**5abb** was already generated although the reaction proceeded moderately (entry 3 or 4). The toluene solvent greatly increased the catalytic activity of Rh/(*S*)-**4**,[11] resulting in a higher rate of 1,2-addition to (*S*)-**1ab**. Therefore, the other solvent was used to suppress the 1,2-addition by deactivating the catalytic activity of Rh/(*S*)-**4**. The reaction in 1,4-dioxane in the presence of 3% Rh/(*S*)-**4** for 1 h was very slow (28% conversion, entry 5). Although the conversion was improved to 66% by increasing the reaction time to 6 h, 15% of (2*S*,4*R*)-**5abb** was generated. The halogenated solvent afforded a better result. The reactions in 1,2-dichloroethane or dichloromethane for 1 h gave moderate yields of (*S*)-**1ab** with small amounts of (2*S*,4*R*)-**5abb** (entry 7 or 8). When the reaction with 5.0 equiv of **3b** was performed, (*S*)-**1ab** was obtained in an 82% yield, and the formation of (2*S*,4*R*)-**5abb** was suppressed to 10% (entry 9). Although the catalytic activity of Rh/(*S*)-**4** decreased as compared with that in toluene (Table 1), nevertheless, it was critically higher than that of previous reports.[9]

Several reactions of arylboronic acid **3** and substituted chromone **2** were performed in dichloromethane in the presence of 1.5% $[RhOH(cod)]_2$ complex (3% Rh) (Table 3). Each of these reactions required the optimization of the reaction conditions (i.e., the amount of **3**, the reaction temperature, and the reaction time) to suppress the formation of the byproduct **5**. Overall, the reactions gave almost optically pure products (*S*)-**1** in yields of over 80% except for the reaction of 7-hydroxychromone (**2f**), which did not dissolve in the solvent (entry 11). When the hydroxy group was protected with MOM, the reaction proceeded smoothly to yield 90% of (*S*)-**1ga** (entry 12). The product (*S*)-**1ga** could be deprotected by treatment with concd HCl in CH_2Cl_2 to yield 88% of (*S*)-**1fa** without loss of optical purity (99% ee).

Table 3. Asymmetric 1,4-Addition of **3** to **2**

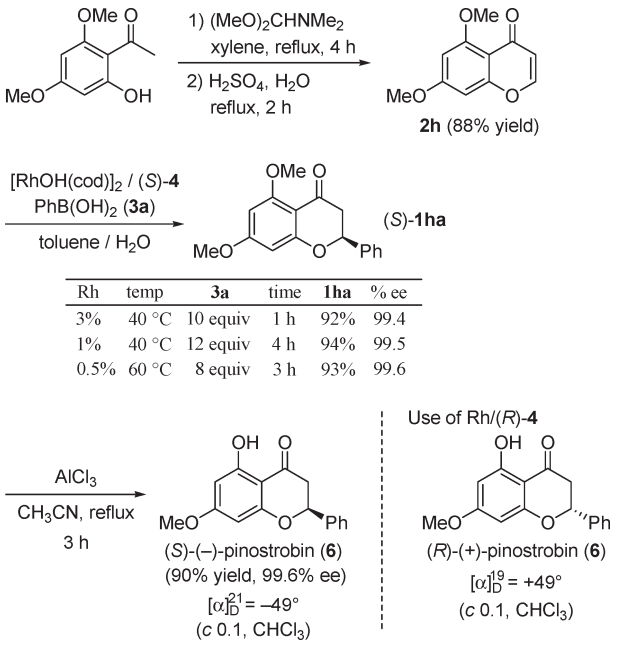


entry	**2**	**3** [equiv]	temp (°C)	**1** (%)[a] [% ee][b]	**5** (%)[a] [% ee][b]
1[f]	**2a**	**3b** [5]	20	**1ab**, 82 [99]	**5abb**, 7 [>99]
2[f]	**2a**	**3c** [3]	20	**1ac**,[c] 90 [>99]	**5acc**,[d] 2 [99]
3[g]	**2a**	**3d** [12]	20	**1ad**,[c] 83 [>99]	**5add**, 0
4[h]	**2a**	**3e** [3]	0	**1ae**, 83 [99]	**5aee**, 3 [99]
5[g]	**2a**	**3f** [15]	10	**1af**,[c] 80 [>99]	**5aff**,[d] 2 [>99]
6[e,g]	**2a**	**3g** [13]	40	**1ag**,[c] 80 [99]	**5agg**,[d] 6 [97]
7[i]	**2b**	**3a** [5]	40	**1ba**,86 [>99]	**5baa**,8 [98]
8[j]	**2c**	**3a** [10]	35	**1ca**, 81 [>99]	**5caa**, 3 [>99]
9[g]	**2d**	**3a** [8]	30	**1da**, 87 [>99]	**5daa**, 6 [>99]
10[i]	**2e**	**3a** [8]	40	**1ea**,[c] 90 [>99]	**5eaa**,[d] 8 [94]
11[g]	**2f**	**3a** [8]	30	**1fa**, 0	**5faa**, 0
12[g]	**2g**	**3a** [8]	30	**1ga**, 91 [99]	**5gaa**, 0

[a] Isolated yield. [b] The enantiomeric excess was determined by chiral HPLC analyses (see the Supporting Information). [c] Absolute configuration was unclear. In all compounds, negative optical rotation was observed. [d] Absolute configuration was unclear ((2*S**,4*R**)-form). [e] In toluene. [f] For 1 h. [g] For 2 h. [h] For 0.7 h. [i] For 1.5 h. [j] For 3 h.

This catalytic system was applicable to the synthesis of (*S*)-(−)-pinostrobin (**6**), which shows many biological activities including antiviral,[18] antioxidant,[19] antileukemic,[20] and antiaromatase[21] activities, is an inhibitor of sodium channel[22] and Ca^{2+} signaling pathways,[23] and inhibits intestinal smooth muscle contractions.[24] Although pinostrobin is an attractive natural product, its procurement almost always relies on extraction from a natural source.[25] There is only one method for the chemical synthesis of optically pure **6** through the intramolecular Mitsunobu reaction of substituted chiral 2-hydroxyphenyl propanone, which was synthesized from a chiral building block.[26] Meanwhile, no efficient synthetic procedure through an asymmetric catalysis has been reported. Therefore, we attempted the synthesis of optically pure **6** through Rh-catalyzed asymmetric 1,4-addition by using Rh/(*S*)-**4** (Scheme 1). Substrate **2h** was easily synthesized from commercially available 4′,6′-dimethoxy-2′-hydroxyacetophenone.[27] The asymmetric 1,4-addition to **2h** with 10 equiv of **3a** was performed using 3% Rh/(*S*)-**4** in CH_2Cl_2 at 40 °C for 2 h. However, **2h** was a less reactive substrate, and the product **1ha** was obtained in low yield (33%). Fortunately, the reaction in toluene yielded 92% of (*S*)-**1ha** (99.4% ee) without the generation of the 1,2-/1,4-adduct because of the steric repulsion of the *o*-methoxy group for the coordination of (*S*)-**1ha** to Rh. The reaction proceeded in the presence of 1% Rh/(*S*)-**4** at 40 °C for 4 h to give 94% of (*S*)-**1ha**. When the reaction was performed at 60 °C for 3 h, the catalyst loading could be decreased to 0.5% to yield 93% of (*S*)-**1ha** with 99.6% ee. Furthermore, the regioselective demethylation of (*S*)-**1ha** with $AlCl_3$ was performed according to the published method[26] to yield 90% of (*S*)-(-)-**6** in a natural form without loss of optical purity (99.6% ee). As a results, (*S*)-(−)-**6** was synthesized in three steps with an overall yield of 74% from commercially available 4′,6′-dimethoxy-2′-hydroxyacetophenone. The unnatural (*R*)-(+)-**6** could be prepared using the (*R*)-**4** ligand in the catalysis of **2h**.

Scheme 1. Synthesis of Optically Pure Pinostrobin (**6**)



Rh	temp	3a	time	1ha	% ee
3%	40 °C	10 equiv	1 h	92%	99.4
1%	40 °C	12 equiv	4 h	94%	99.5
0.5%	60 °C	8 equiv	3 h	93%	99.6

In summary, we have developed a method for the highly enantioselective synthesis of flavanones through the Rh-catalyzed asymmetric 1,4-addition. This method promises to make the preparation of bioactive chiral flavanones easy from commercially available chromones or arylboronic acids. As a typical example, (*S*)- and (*R*)-pinostrobin could be efficiently synthesized through asymmetric catalysis. The synthesis was achieved using the rhodium catalyst with highly electron-poor chiral diphosphine MeO-F_{12}-BIPHEP. This catalyst would be widely applicable to the synthesis of other bioactive chiral compounds through the asymmetric 1,4-addition.

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Supporting Information Available. Experimental procedures, spectroscopic data, copies of NMR spectra and HPLC, and confirmation of relative conformation of **5aaa** by NOE (NOESY) experiments and DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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