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Rhodium-Catalysed Asymmetric Synthesis of 4-Alkyl-4*H*-Chromenes

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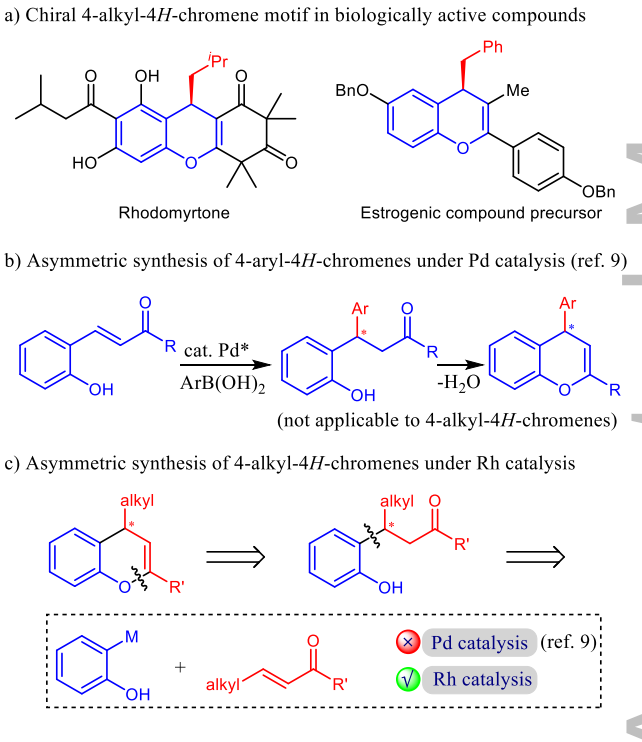
Abstract. A general method for the catalytic asymmetric synthesis of 4-alkyl-4*H*-chromenes was developed. With readily available β-alkyl-substituted enones and 2-hydroxylated arylboronic acids, a rhodium-catalysed asymmetric conjugate addition/intramolecular hemi-acetalization/acid-promoted dehydration sequence leads to the formation of 4-alkyl-4*H*-chromenes in up to 99% yield and with up to >99% ee. The current study remedies the methodological deficiency in asymmetric synthesis of 4-alkyl-4*H*-chromenes.

Keywords: asymmetric synthesis; 4*H*-chromene; arylboronic acid; catalysis; rhodium

Chromenes (also called benzopyrans) are fundamental structures found in numerous natural products and biologically active compounds.[1] In particular, chiral 4*H*-chromenes are highly useful in medicinal and synthetic chemistry.[2] Given the importance of this privileged chiral structure, considerable efforts have been devoted to developing versatile methods for their asymmetric synthesis.[3] Over the past decades, various approaches such as asymmetric nucleophilic addition to benzopyrylium ion,[4] asymmetric trapping of *ortho*-quinone methide,[5] and intermolecular cyclization under asymmetric iminium-allenamine catalysis,[6] among other,[7] have been successfully developed to achieve a series of chiral 4*H*-chromenes. Despite the merits of these approaches, the existing strategies are generally not applicable to the synthesis of 4-alkyl-4*H*-chromenes. The 4-alkyl substitutions on 4*H*-chromenes are essential for biologically active targets (Scheme 1a),[8] thus development of a general method for asymmetric synthesis of 4-alkyl-4*H*-chromenes would be highly beneficial for applications in target-oriented synthesis.

The chromene structure can be readily generated by an intramolecular cyclodehydration reaction from the β-phenolic ketones (Scheme 1c), so the key is how to efficiently construct such a chiral phenolic intermediate. As a pioneering work, Miyaura and co-workers reported the palladium-catalysed asymmetric conjugate addition of arylboronic acids to 2-hydroxyarylidene ketones to give β-phenolic ketones, which underwent intramolecular cyclodehydration to give chiral 4*H*-chromenes (Scheme 1b).[9] However, this reaction system only worked for the synthesis of 4-aryl-4*H*-chromenes. To achieve the synthesis of 4-alkyl-4*H*-chromenes, a different catalytic system that could enable the efficient generation of chiral β-alkyl-β-phenolic ketones should be introduced.

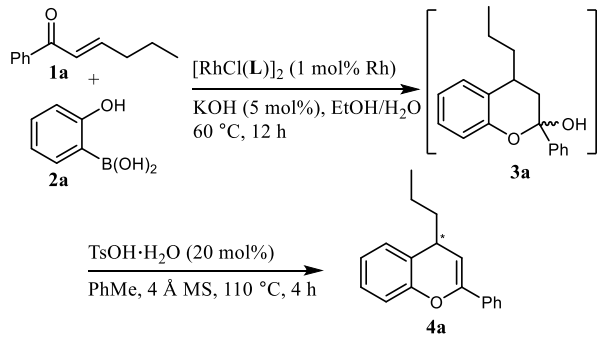


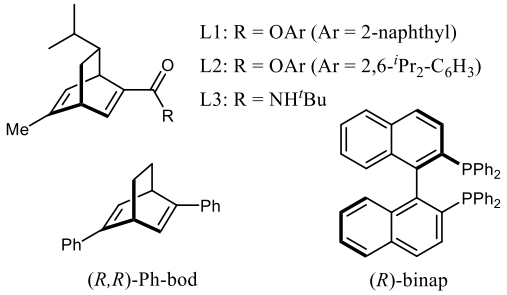
Scheme 1. Importance and asymmetric synthesis of 4-alkyl-4*H*-chromenes.

The rhodium-catalysed asymmetric conjugate addition of arylboronic acids to enones has emerged as a reliable method for synthesizing chiral molecules.[10] Early studies showed that phenol deactivated the rhodium catalyst,[11] thus hydroxylated arylboronic acids have been rarely employed under rhodium catalysis.[12] Recently, we proved the compatibility of hydroxylated arylboronic

acids with rhodium catalyst in ethanol.[13] In this context, we considered addressing the aforementioned issue using the combination of 2-hydroxylated arylboronic acids and β-alkyl enones under rhodium catalysis. As part of our ongoing efforts on the synthesis of important structures under rhodium catalysis,[14] we herein report that the rhodium catalyst efficiently promoted the asymmetric conjugate addition of 2-hydroxylated arylboronic acids to β-alkyl enones, and a general method for the synthesis of chiral 4-alkyl-4*H*-chromenes via a rhodium-catalysed asymmetric conjugate addition/intramolecular hemiacetalization/ acid-promoted dehydration process was successfully developed.

Table 1. Optimization for the asymmetric synthesis of chiral chromene from β-alkyl enone **1a** and 2-hydroxylated phenylboronic acid **2a**.[a]





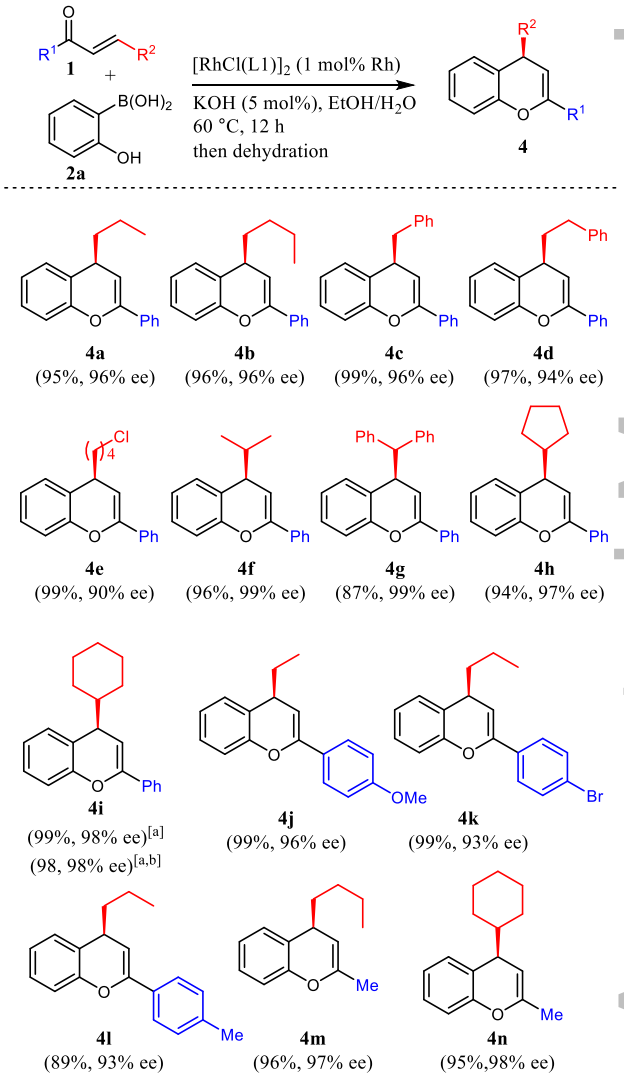
Entry	Reaction conditions	Yield [%][b]	ee [%][c]
1	L1 as ligand	95	96
2	L2 as ligand	86	93
3	L3 as ligand	90	81
4	(*R*,*R*)-Ph-bod as ligand	85	71
5	(*R*)-binap as ligand	14	87
6	L1, THF instead of EtOH	95	95
7	L1, toluene instead of EtOH	96	95

[a] Conditions for Rh-catalysed addition: **1a** (0.20 mmol), **2a** (0.40 mmol), [RhCl(L)]$_2$ (1 mol% Rh), and KOH (5 mol%) in EtOH/H$_2$O (1.0 mL/0.1 mL) at 60 °C for 12 h. Conditions for dehydration: crude **3a**, TsOH·H$_2$O (20 mol%), and 4 Å MS (200 mg) in toluene (3.0 mL) at 110 °C for 4 h.

[b] Isolated yield of **4a**.

[c] The ee value of **4a** was determined by HPLC analysis on a chiral stationary phase.

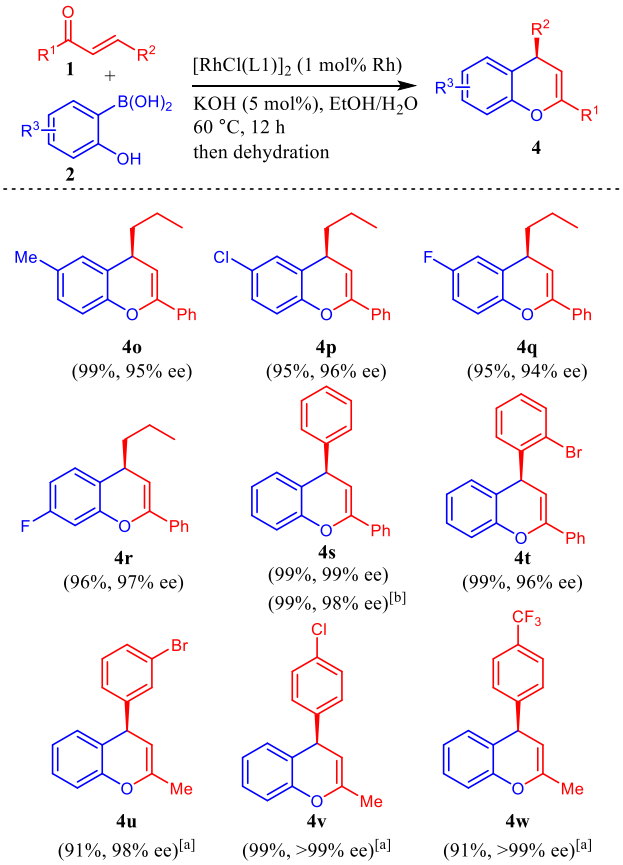
We embarked on the investigation from the model reaction between 2-hydroxylated phenylboronic acid **2a** and β-alkyl enone **1a**. The synthesis involves a two-step sequence: chiral rhodium catalyst was used to control the formation of the new stereogenic center, and the hemiacetal intermediate **3a** was dehydrated to give the desired 4-alkyl-4*H*-chromene **4a**. As summarized in Table 1, chiral diene-ligated rhodium catalysts showed high reactivity for the reaction (entries 1–4), and easily prepared chiral diene L1[15] proved to be the best to give **4a** in a high yield with 96% ee. In contrast, the bisphosphine (*R*)-binap-ligated rhodium catalyst showed a much lower reactivity (entry 5), validating the importance of the diene ligand.[16] In addition to ethanol, the reaction also proceeded well in other solvents like THF and toluene (entries 6–7), although the enantioselectivity was slightly lower.



Scheme 2. Substrate scope of β-alkyl enones. [a] 2 mol% Rh and 3 equiv. of **2a** were used in EtOH at the conjugate addition step. [b] Conducted on 1.0 mmol scale.

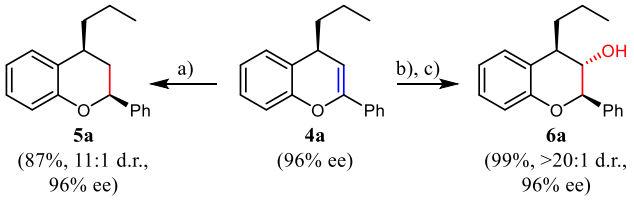
With the conditions in entry 1 of Table 1 as the optimal conditions, the scope of the asymmetric synthesis of chiral 4-alkyl-4*H*-chromene was then studied. The generality of β-alkyl enones was first

investigated, and the results were summarized in Scheme 2. The established method worked well to give chiral 4*H*-chromenes bearing a variety of 4-alkyl substitutions in high yields and with good to excellent enantioselectivities (87%–99% yield, 90%–99% ee). For instance, linear alkyl substitutions with different chain length, including those bearing aryl and halogen groups, all worked well (**4a**–**4e**). The sterically hindered alkyl substitutions (**4f**–**4g**) and cycloalkyl substitutions (**4h**–**4i**) were all well tolerated. Furthermore, substitutions on the 2-position of 4*H*-chromene products were amendable to both aryl and alkyl groups (**4j**–**4n**).



Scheme 3. Scope of hydroxylated arylboronic acids and enones. [a] 10 mol% acid was used at the dehydration step. [b] Conducted on 1.0 mmol scale.

As shown in Scheme 3, 2-hydroxylated arylboronic acids bearing different substitutions can be used to generate substituted chiral 4-alkyl-4*H*-chromenes (**4o**–**4r**), without affecting the yields and enantioselectivities. In addition, the feasibility of the current method for the synthesis of chiral 4-aryl-4*H*-chromenes was tested, and we were delighted to see that 4-aryl-4*H*-chromenes (**4s**–**4w**) were attainable in high yields and with excellent enantioselectivities by using β-aryl enones under the established reaction conditions.[17] However, the current method is not applicable to the synthesis of 4,4-disubstituted chromenes, as the rhodium-catalysed conjugate addition step showed very low reactivity for β,β-disubstituted enones.



Scheme 4. Synthetic transformations of chromene **4a**. a) Pd/C, H_2, rt. b) BH_3, THF, 0 °C. c) H_2O_2, NaOH, 60 °C.

The synthetic transformation of the 4-alkyl-4*H*-chromene product was illustrated in Scheme 4. Chromene **4a** was readily hydrogenated to the corresponding chromane **5a**, and chroman-3-ol **6a** was easily obtained quantitatively by the standard hydroboration/oxidation procedure. It is noteworthy that high diastereoselectivity was observed for both transformations.

In summary, we have developed the first general method for the asymmetric synthesis of 4-alkyl-4*H*-chromenes. The key to success is the asymmetric addition of 2-hydroxylated arylboronic acids to enones enabled by rhodium catalysis. The developed method features low catalyst loading, excellent enantiocontrol, and broad substrate scope, and it shall find broad applications in target-oriented synthesis of chiral chromene derivatives.

Experimental Section

General Procedure for the Asymmetric Synthesis of 4-Alkyl-4*H*-Chromenes

$[RhCl(L1)]_2$ (0.9 mg, 1 μmol, 1 mol% Rh), enone **1** (0.20 mmol), and 2-hydroxylated arylboronic acid **2** (0.40 mmol) were placed in a Schlenk tube under nitrogen. EtOH (1.0 mL) and aqueous KOH (0.1 mL, 0.1 M, 5 mol%) were added and the resulting solution was stirred at 60 °C for 12 h. Upon completion, the reaction solution was diluted with water (5 mL) and extracted with EtOAc (5 mL*3). The combined organic layer was passed through a short pad of silica gel, and the solvent was removed under vacuum to give the crude intermediate. The intermediate was directly dissolved in toluene (3.0 mL), and $TsOH \cdot H_2O$ (20 mol%) and 4 Å MS (200 mg) were then added. The resulting mixture was stirred at 110 °C for 4 h. Upon completion, the mixture was subjected to silica gel chromatography with petroleum ether to petroleum ether/EtOAc (v/v = 10/1) to give the chromene product **4**.

Acknowledgements

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[17] The absolute configuration of product **4s** was assigned by comparison of its specific rotation with that reported, see SI for details.

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COMMUNICATION

Rhodium-Catalysed Asymmetric Synthesis of 4-Alkyl-4*H*-Chromenes

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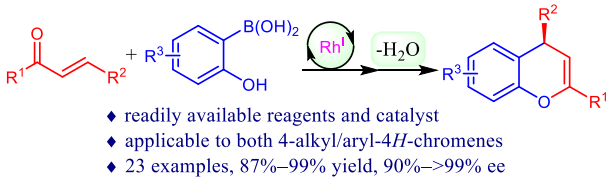

- readily available reagents and catalyst
- applicable to both 4-alkyl/aryl-4*H*-chromenes
- 23 examples, 87%–99% yield, 90%–>99% ee