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Synthesis of chiral chromanols *via* a RuPHOX–Ru catalyzed asymmetric hydrogenation of chromones†

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Chiral chromanols and their derivatives have been synthesized *via* a RuPHOX–Ru catalyzed asymmetric hydrogenation of chromones in high yields, >20 : 1 drs and with up to 99.9% ee. Control experiments show that the reaction undergoes two sequential asymmetric hydrogenation steps of the C=C and C=O double bonds. The reaction could be performed on a gram-scale with a relatively low catalyst loading (up to 1000 S/C), and the resulting products can be transformed to several biologically active compounds.

The chromanoid structural motif is found in numerous well-known natural products, drug candidates and biologically active molecules.[1] The subgroups of chromanoids, that is chromanones and chromanols, also exhibit antidiabetic, antibacterial, antioxidant, antiestrogenic activities.[2] They can most likely be selected as alternative chiral counterparts of chromones for the development of new drugs which may possess a broader spectrum of biological activities. Therefore, the development of these chiral subgroup motifs *via* an efficient synthetic procedure is worthwhile.

From the viewpoint of convenient derivatization, the direct synthesis of chiral chromanols is interesting because the hydroxyl group can either partake in asymmetric nucleophilic substitution for the preparation of other drugs and drug candidates, be oxidized to chromanones or reduced to chromanes (Fig. 1, up). Chiral chromanols themselves and their derivatives are all useful skeletons, existing in many natural products (Fig. 1, down). Current methodologies mainly afford chiral chromanones through the asymmetric hydrogenation of chromones.[3] Only a handful of examples have focused on the direct synthesis of chiral chromanols and their flavanol analogues (Scheme 1).[4] Wang *et al.* established an efficient chiral BINOL-Ti(Oi-Pr)$_4$-catalyzed reaction of tertiary enamides with salicylaldehydes under mild conditions to afford diverse 4-chromanol derivatives in high yields with excellent *enantio*- and diastereoselectivity.[4a] Metz *et al.* reported a kinetic resolution of racemic flavanones with a Rh(III) complex catalyzed asymmetric transfer hydrogenation, producing chiral flavanones and flavanols in high yields and with excellent enantioselectivities.[4b] Ashley, Sherer and coworkers discovered a unique combination of a base-catalyzed β-epimerization and ruthenium-catalyzed asymmetric transfer hydrogenation that enables the facile reductive dynamic kinetic resolution of β-substituted chromanones.[4c] In 2013, the Glorius group developed an asymmetric hydrogenation of 2-substituted flavones and chromones using a chiral ruthenium–NHC complex, leading to the formation of chiral flavanones, flavanols, chromanones, and chromanols.[4d] Full conversion and excellent enantioselevtivities, but low diastereoselectivities, were obtained under high hydrogen pressure (120–150 bar). The asymmetric hydrogenation of chromanones is one of the most efficient methods for the synthesis of chiral chromanols because of its high efficiency, environmental friendliness, and low economic cost.[5] Therefore, an efficient asymmetric hydrogenation of chromones for the direct synthesis of chiral chromanols with excellent diastereoselectivities is highly desired.

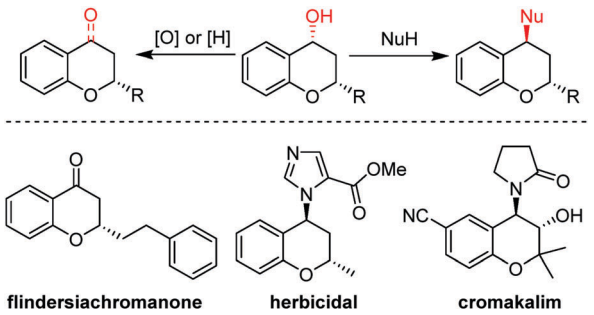

Fig. 1 Chiral chromanols and their derivatives.

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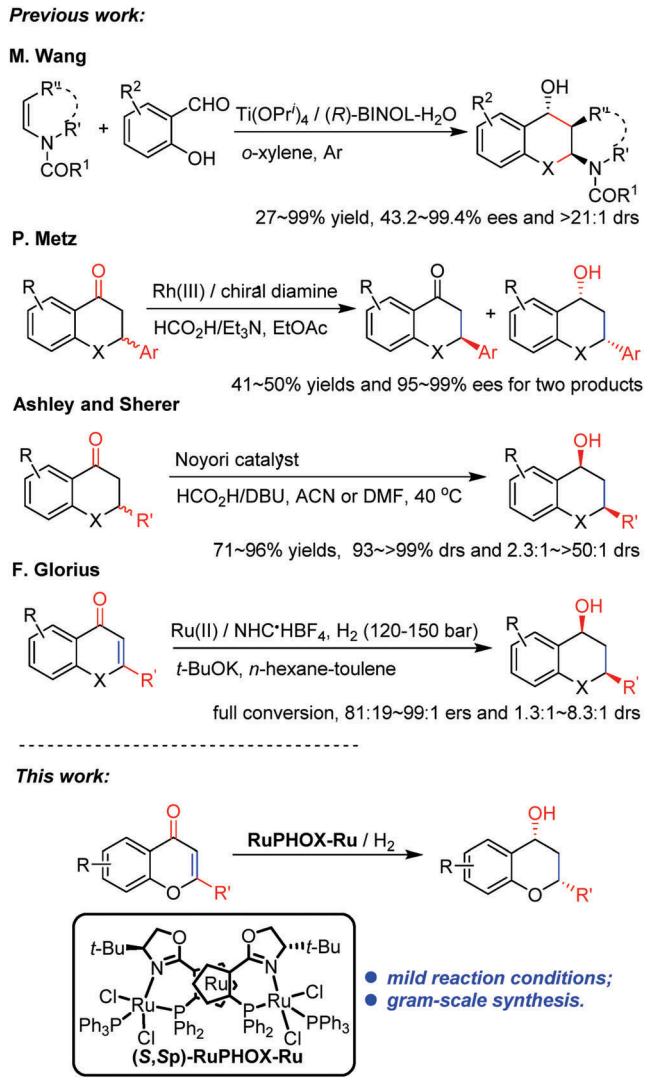


Scheme 1 Asymmetric synthesis of chiral chromanols.

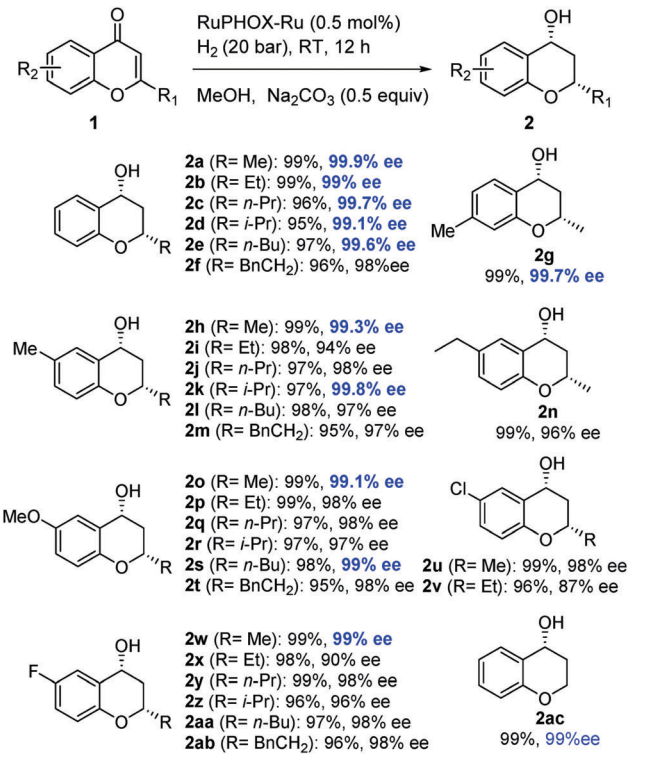
We have previously reported the development of a readily accessible ruthenocenyl phosphino-oxazoline–ruthenium complex (RuPHOX–Ru) bearing dual catalytic centers, which has shown promising catalytic activity in many asymmetric reactions.[6,7] Specifically, this complex has been employed as a chiral catalyst for the asymmetric hydrogenation of various C=C and C=O double bonds, providing the corresponding products in up to 99% yield and 99.9% ee.[7] Encouraged by these promising results, we herein report the efficient and mild RuPHOX–Ru catalyzed asymmetric hydrogenation of chromones for the direct synthesis of chiral chromanols (Scheme 1).

Initially, the RuPHOX–Ru catalyzed asymmetric hydrogenation of 2-methyl-4*H*-chromen-4-one (chromone **1a**) was carried out in the presence of Cs_2CO_3 under a certain hydrogen pressure in different solvents at room temperature. It was found that the best results were obtained when 20 bar hydrogen pressure was used in either MeOH or toluene as a solvent.[8] Subsequently, we chose both MeOH and toluene as the solvents to examine the impact of different bases on the reaction (Table S2, ESI†).[8] Thus, the optimal reaction conditions were found to be the following: using Na_2CO_3 as a suitable base in MeOH under 20 bar hydrogen pressure at room temperature over 12 h.

With the optimized reaction conditions in hand, substrates bearing different 2-position and aryl substituents were then investigated (Table 1). First, substrates 2 with different alkyl substituents at the 2-position were examined and the desired products were obtained in high yields and almost >99% ee (**2a–2f**). When an electron-donating Me group was present at the 7 and 8-position, high yields and excellent enantioselectivities were still obtained (**2g** and **2h**). The counterparts of **2h** bearing different alkyl groups at the 2-position were examined and excellent asymmetric behaviors were observed (**2i–2m**). When an Me group was replaced by other electron-donating groups, *e.g.* Et and MeO, the desired products were still obtained in quantitative yields and 96–99% ees (**2n–2t**). Replacing the electron-donating substituents with electron-withdrawing groups such as Cl or F had little effect on the reaction, with the corresponding products being obtained with more than 98% ee in many cases (**2u–2ab**). Finally, a substrate lacking a 2-substituent was examined. To our delight, the desired product **2ac** was obtained in 99% yield and with 99% ee.

To examine the efficiency of the catalyst system, a gram-scale hydrogenation of **1a** (1.87 g) was carried out with a low catalyst

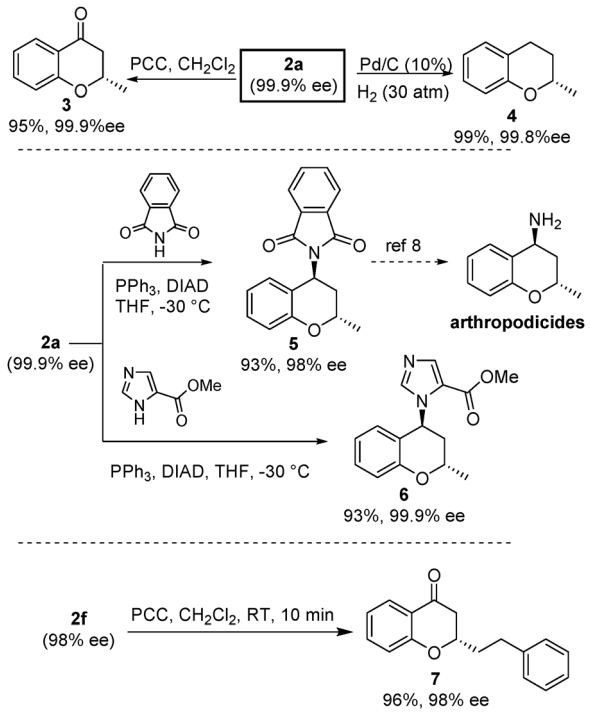
Table 1 Scope of substrates[a]



[a] Using the optimal reaction conditions shown in Table S2 (entry 2, ESI); ees were determined by chiral HPLC analysis of **2** using an OD-H and AS-H column; Drs were determined by ^{1}H NMR with >20 : 1 in all cases; the absolute configurations of **2** were determined by analogy according to **2a** which was determined by the X-ray diffraction of its single crystal and is shown in Table S2 (ESI).[8,9]

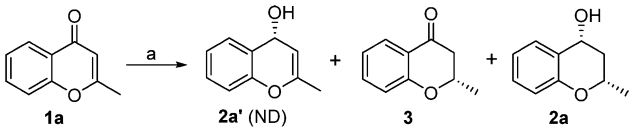
loading of 0.1 mol% (S/C = 1000) with modified reaction conditions under 50 bar H_2 at room temperature over 12 h. The desired product **2a** was obtained in 99% yield and with 96% ee.[8] Chiral chromanols **2** are important building block and can be transformed into a number of different biologically active compounds (Scheme 2). Thus, the oxidation of **2a** could be performed to afford the corresponding chromanone product **3** or be dehydroxylated by Pd/C and H_2 to give chromane **4** without any effect on enantioselectivities (Scheme 2, top). Alternatively, the hydroxyl of **2a** can replaced by *o*-phthalimide to give **5** with the opposite configuration *via* a Mitsunobu reaction in the presence of PPh_3 and DIAD.[8,9] **5** could be hydrolyzed with hydrazine hydrate to produce an arthropodicide according to a reported method.[10] Similarly, a herbicidal **6** was obtained in 93% yield and with 98% ee *via* a Mitsunobu reaction with methyl 5-imidazolecarboxylate (Scheme 2, middle).[2c] Additionally, the oxidation of **2f** using PCC in DCM over 10 min afforded the natural product flindersiachromanone **7**, which can be isolated from the extracts of the bark of *Flindersia laevicarpa* (Scheme 2, bottom).[2a]

In order to gain a better insight into the reaction process, a series of control experiments were conducted. The reactions were quenched at different times (Table 2), and the reaction mixtures were analysed by ^{1}H NMR spectroscopy. No intermediate **2a′** relating to the hydrogenation of the C=O double bond was formed; however, an intermediate **3** was observed corresponding to the hydrogenation of the C=C double bond. It was obvious that the hydrogenation of C=C double bond is fast and the amount of **1a** decreases sharply (almost disappeared after 4 h, entries 1–5).[11] The subsequent hydrogenation of the C=O double bond of **3** quickly gives the desired product **2a** and the reaction goes to completion within 12 h (entries 6 and 7).



Scheme 2 Transformation of chromanol and application.

Table 2 Screening of reaction time[a]



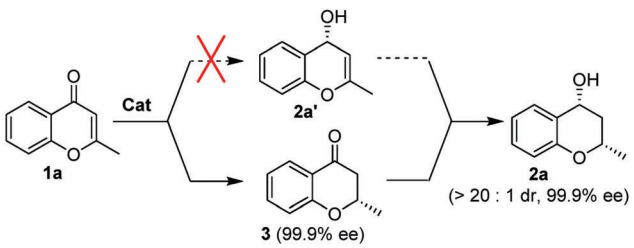
Using the optimal reaction conditions: a) RuPHOX-Ru (0.5 mol%), MeOH, Na_2CO_3 (0.5 equiv), H_2 (20 bar), RT, 12 h

Entry	Time/h	**1a**/**3**/**2a**[b] (%)
1	0.25	93.7/4.2/2.1
2	0.5	87.7/6.6/5.7
3	1	62.8/16.3/20.9
4	2	8.5/6.8/84.7
5	4	1.9/2.9/95.2
6	6	1.0/2.9/96.1
7	12	0/0/100

[a] Using the optimal reaction conditions shown in Table S2 (entry 2, ESI). [b] Determined by ^{1}H NMR.

To further verify the above reaction pathway, we prepared chiral intermediate **3** in 99.9% ee using the abovementioned method (Scheme 2, top), which was subjected to the asymmetric hydrogenation using the optimal reaction conditions shown in Table S2 (ESI†) (entry 2). As expected, the desired product **2a** was obtained in quantitative yield and high diastereoselectivity (>20 : 1 dr) and no erosion in enantioenrichment (99.9% ee, Scheme 3). Combined with the control experimental results above, the asymmetric hydrogenation of chromone **1a** presumably undergoes the following sequential steps (Scheme 3): originally, the C=C double bond, rather than the C=O double bond of **1a**, is reduced, affording the chiral chromanone **3** quickly. Then, the asymmetric hydrogenation of the C=O double bond of **3** proceeds to deliver the desired product **2a**. It should be noted that the asymmetric catalytic hydrogenation of **3** proceeds together with a certain extent of dynamic kinetic resolution process.[4c,8]

In summary, we have developed a RuPHOX–Ru catalyzed asymmetric hydrogenation of chromones for the synthesis of chiral chromanols and their derivatives. Under the optimal reaction conditions, almost quantitative yields, >20 : 1 drs and up to 99.9% ees were obtained for all examples. The control experiments showed that the asymmetric hydrogenation of the C=C double bond occurs first followed by the reduction of the C=O double. The reaction could be performed on a gram-scale with a relatively low catalyst loading (up to 1000 S/C), and the resulting products can be transformed to several biologically active compounds.



Scheme 3 The possible reaction pathway.

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Conflicts of interest

There are no conflicts of interest to declare.

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