Asymmetric Hydrogenation

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Ruthenium–NHC-Catalyzed Asymmetric Hydrogenation of Flavones and Chromones: General Access to Enantiomerically Enriched Flavanones, Flavanols, Chromanones, and Chromanols**

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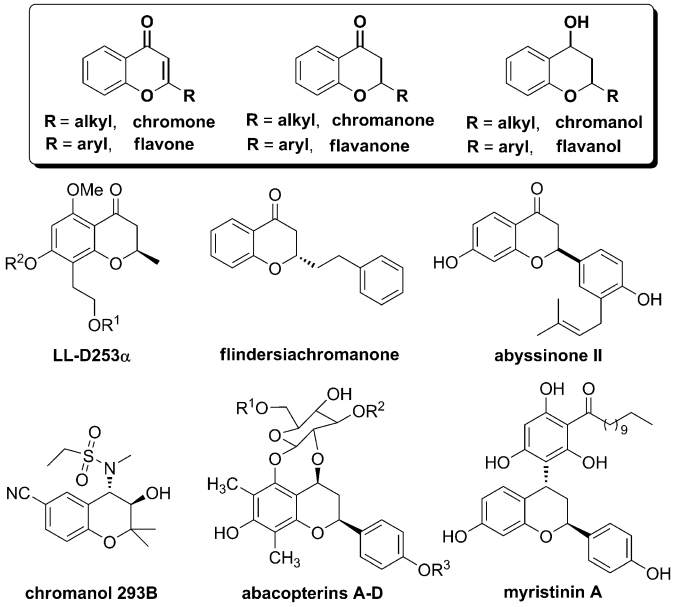
Dedicated to Professor Ryoji Noyori on the occasion of his 75th birthday

Flavanoids and chromanoids including flavanones, flavanols, chromanones, and chromanols are a large family of well-known natural products (Scheme 1).[1,2] These natural products have been shown to exhibit a wide range of biological activities including anticancer, antitumor, antibacterial, antimicrobial, antioxidant, estrogenic, and antiestrogenic properties. Additionally, these chiral flavanoids and chromanoids could readily be utilized in the synthesis of many benzopyran-containing natural products by established reaction pathways (Scheme 1).[3]

Although there are numerous reports on the synthesis of flavanones, flavanols, chromanones, and chromanols, only few stereoselective methods have been devised to access enantiomerically enriched products.[4] In fact, to the best of our knowledge, so far no transition-metal-catalyzed method has been reported for the highly enantioselective synthesis of 2-substituted flavanols and chromanols despite their importance.[2e,5] Owing to minimal negative environmental impact, high atom economy, and operational simplicity, the transition-metal-catalyzed asymmetric hydrogenation has long held a respected position both in academia and in industry for the preparation of optically active compounds.[6,7] However, even though the enantioselective hydrogenation of natural and commercial chromones and flavones seems to be one of the most straightforward ways to synthesize flavanones, flavanols, chromanones, and chromanols, the asymmetric catalytic hydrogenation of chromones[8] and flavones remains largely unexplored.[9] It would be highly desirable to develop a general, efficient catalytic system for the asymmetric hydrogenation of these heterocycles.



Scheme 1. Representative structures of biologically active flavanoid and chromanoid natural products.

During the course of our investigation into the asymmetric hydrogenation of (hetero)arenes, we found that the combination of ruthenium(II) and several NHCs (NHC = N-heterocyclic carbene) led to the formation of highly active and enantioselective catalysts for the hydrogenation of quinoxalines, benzofurans, and (benzo)thiophenes.[7n,o,10] In light of the high level of reactivity and enantioselectivity of our Ru–NHC catalyst, we rationalized that chromones and flavones could be hydrogenated directly to flavanols and chromanols in a stereoselective manner. Further we could easily obtain the enantiomerically enriched flavanones and chromanones by a simple and selective subsequent oxidation.[11] Herein we report the first asymmetric hydrogenation of chromones and flavones using a chiral NHC–Ru complex. This direct and general route is capable of accessing biologically active enantiomerically enriched flavanoids and chromanoids comprising all the above-mentioned structures: flavanones, flavanols, chromanones, and chromanols (Scheme 2).

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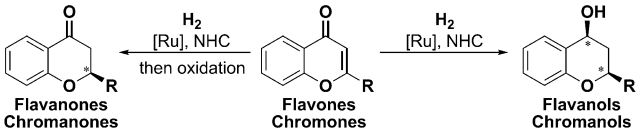


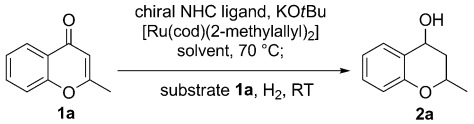
Scheme 2. Hydrogenation of chromones and flavones to optically active flavanones, flavanols, chromanones, and chromanols.

We commenced our study with the hydrogenation of 2-methyl-4*H*-chromen-4-one (**1a**) to optimize the reaction conditions. Fortunately, when we applied our Ru catalyst formed from ICy·HCl (**3a**; ICy = *N*,*N*′-dicyclohexylimidazol-2-ylidene) for the hydrogenation of **1a**, we exclusively obtained the corresponding 2-methyl-4*H*-chroman-4-ol (**2a**) with a d.r. of 1:1 (Table 1, entry 1). Encouraged by this result, we tested whether our previously developed chiral ruthenium–NHC complex, formed from the imidazolinium salt **3b**, could control the diastereoselectivity and enantioselectivity in the hydrogenation of **1a**. When we submitted **1a** to the hydrogenation process at 80 bar of H_2 and 60 °C, the desired product **2a** was formed with full conversion, low diastereoselectivity (d.r. = 1.2:1), and good enantioselectivity (for the major product, e.r. = 93:7) (Table 1, entry 2). We subsequently screened a variety of NHC ligands, solvents, pressures, and temperatures. NHC ligand derived from **3b** proved to be an excellent ligand and the mixture of hexane/toluene (2:1) was clearly the best choice of solvent for inducing enantioselectivity and increasing the reactivity (Table 1, entries 3–9). Generally, we found that lower temperature and higher hydrogen pressure improved the diastereomeric ratio. Finally, we could obtain a good diastereomeric ratio (5:1) and excellent enantioselectivity at 5 °C under 120 bar of H_2 with 5 mol % of catalyst (Table 1, entry 9). Furthermore, the ratio could be elevated to 9:1 after recrystallization. By comparison of the NMR spectrum of **2a** with known compounds, the main product was determined to be *cis*-configured.

With optimized conditions in hand, we tested a variety of 2-substituted flavones and chromones to gain insight into the versatility of our catalytic system (Scheme 3). Fortunately, for most of the 2-alkyl-substituted chromones including many with primary and secondary alkyl chains, the reaction proceeds with full conversion, moderate to good diastereoselectivity, and high enantioselectivity for the major product (Scheme 3, **1a**–**i**). We noticed that the diastereomeric ratio decreased slightly when the length or substitution of the chain was increased, while full conversion to the desired product was maintained. Furthermore, we studied the influence of the substitution on the carbocyclic ring of the chromone (**1h**, **1i**). In these cases good diastereoselectivity and high enantioselectivity were observed, as well. Changing the position of the substituent to position 3 (**1q**) led to a drop in enantioselectivity but full conversion and higher diastereoselectivity (8.3:1) than with the regioisomer **1a**. Our method could also be applied in the hydrogenation of thiochromenone (**2r**).

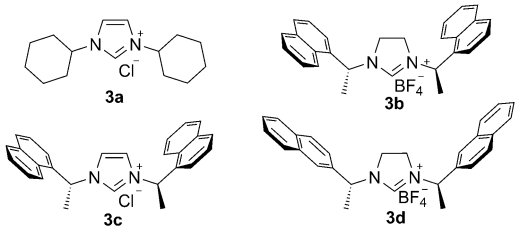
When 2-substituted flavones were employed as substrates, we surprisingly found that only small amounts of the desired hydrogenated products were formed under the above-mentioned conditions. Fortunately, the hydrogenation of flavone **1j** proceeded smoothly with full conversion and good enantioselectivity to give the flavanol **2j** when the reaction was conducted with 10 mol % of catalyst at room temperature. As shown in Scheme 3, under the modified conditions, in most cases, the reaction of 2-substituted flavones gave the desired flavanols in high yields and good enantioselectivity for the *cis* product. We found that the reactivity changes only slightly with the electronic properties of the substituents: When the phenyl ring bears electron-withdrawing groups or electron-rich groups, such as fluorine (**1m**), trifluoromethyl (**1n**), and methoxy (**1o**) in *para*

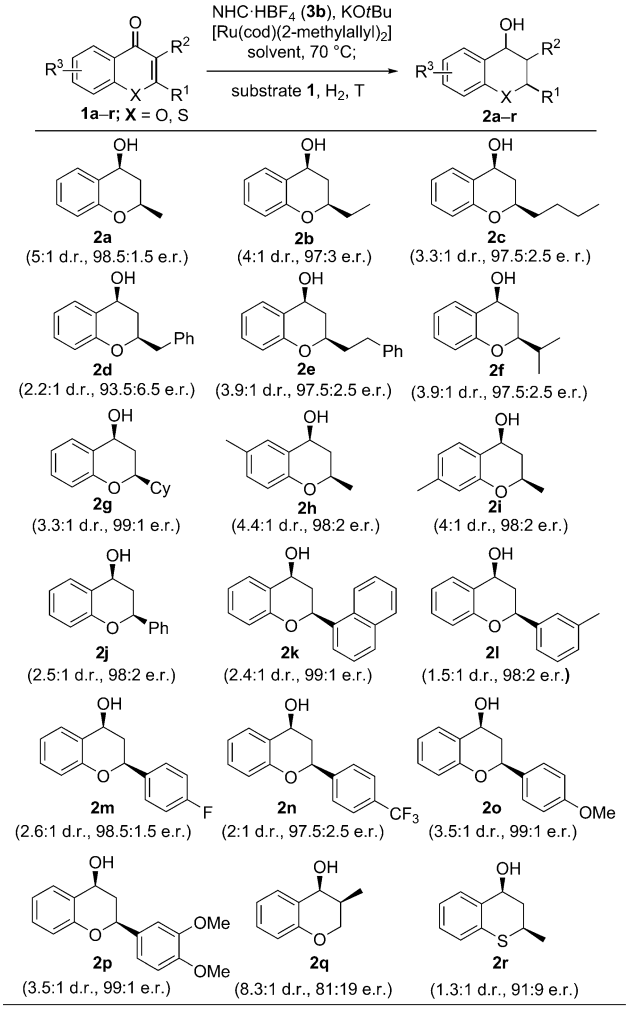
Table 1: Optimization of the reaction conditions for the asymmetric hydrogenation of 2-methyl-4*H*-chromen-4-one (**1a**).[a]



Entry	L	*T* [°C]	*p*(H_2) [bar]	Solv.	d.r.[b]	e.r.[c]	Yield[d] [%]
1	**3a**	60	80	tol.	1:1	–	>99
2	**3b**	60	80	tol.	1.2:1	93:7	>99
3	**3b**	25	80	tol.	2.5:1	95.5:4.5	>99
4	**3c**	25	80	tol.	1.8:1	92:8	>99
5	**3d**	25	80	tol.	–	–	trace
6	**3b**	25	80	hex.	2.7:1	97:3	>99
7	**3b**	25	120	hex.	3.0:1	97:3	>99
8[e]	**3b**	5	120	hex.	4.5:1	98:2	51%
9[e]	**3b**	5	120	hex./tol. (2:1)	5:1 (9.3:1)[f]	98.5:1.5	>99

[a] General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.015 mmol), KO*t*Bu (0.045 mmol), and NHC ligand (0.03 mmol) were stirred at 70 °C in toluene or hexane (2 mL) for 16 h, after which the reaction mixture was added to **1a** (0.3 mmol), and hydrogenation was performed under the conditions listed in each case for 24 h. [b] d.r. was determined by ^{1}H NMR analysis. [c] e.r. given for main product was determined by HPLC on a chiral stationary phase. [d] Yields pertain to isolated product. [e] The reaction time was prolonged to 36 h. [f] After recrystallization from *n*-hexane/*i*PrOH; tol. = toluene, hex. = hexane.

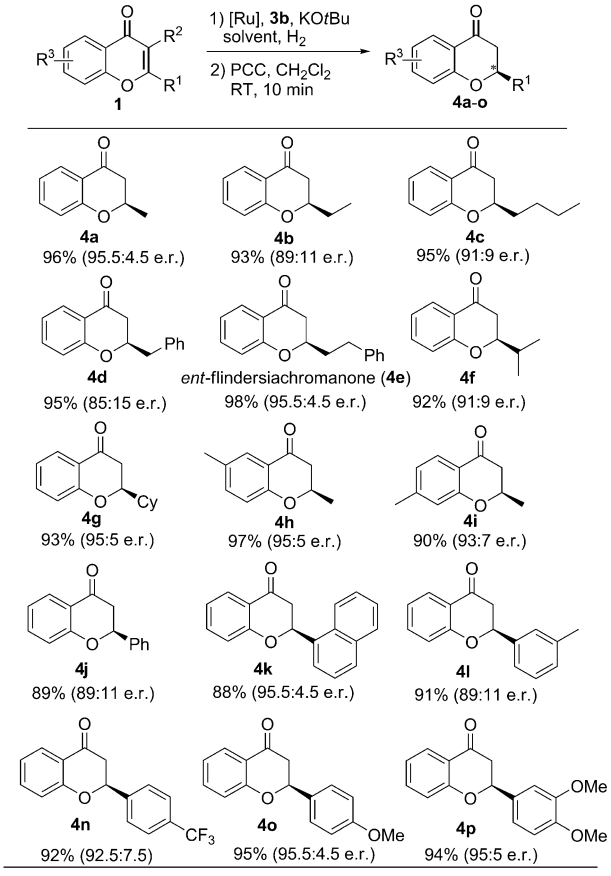




Scheme 3. Catalytic asymmetric hydrogenation of chromones and flavones. General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.015 mmol), KO*t*Bu (0.045 mmol), and NHC ligand (0.03 mmol) were stirred at 70 °C in *n*-hexane (2 mL) for 16 h, after which the reaction mixture was added to **1** (0.15–0.3 mmol) and toluene (1 mL). Then hydrogenation was performed under 120–150 bar of H_2 at 5–25 °C for 36 h. For experimental details see the Supporting Information; d.r. was determined by ^{1}H NMR analysis; e.r. given for main product was determined by HPLC on a chiral stationary phase; full conversion was obtained in all cases, except for **2r** (92% conversion). Cy = cyclohexyl.

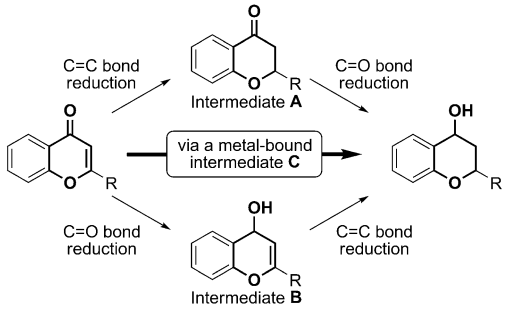
position, the reaction proceeds smoothly at room temperature, with full conversion and very good enantiomeric ratio. We also studied the effect of the substitution pattern of the 2-phenyl ring on the reactivity. The reaction worked nicely for the 2-(1-naphthyl)- (**1k**) and 2-(*m*-tolyl)-substituted flavone (**1l**) with full conversion and excellent enantiomeric ratio. It is worth noting that even though only low to moderate diastereoselectivity could be obtained, to our knowledge, this is the first report of asymmetric hydrogenations of flavones. These enantiomerically enriched, substituted flavanols could provide access to many different chiral frameworks known from natural products.[3]

One of the key aspects of the process is that after hydrogenation, these chiral flavanols and chromanols can be further transformed into a variety of enantiomerically enriched flavanones and chromanones in high yields by simple selective oxidation in the presence of pyridindium chlorochromate (PCC) without compromising the integrity of the newly formed stereocenter at C2 (Scheme 4). Because of the cleanly proceeding hydrogenation process and the high efficiency of selective oxidation, the enantiomerically enriched flavanone and chromanone products could be obtained in analytically pure form by simple filtration. For example, exposure of **2a** to PCC in CH_2Cl_2 at room temperature affords the corresponding chromanone **4a** with an e.r. of 96:4. Although the flavanol and chromanol products are formed as mixtures of *cis* and *trans* diastereomers with our catalytic system, the oxidation generally delivers highly enantiomerically enriched flavanones and chromanones with a variety of aryl/alkyl groups at the C2 position in excellent yields (Scheme 4, **4a**–**o**). In contrast, the previously reported nonhydrogenation-based asymmetric route to these products afforded enantiomerically enriched 2-alkyl chromanones in only low yield if at all.[4f,h,i] By comparison of the optical rotation data of **4a** and **4j** with literature data, the absolute configuration of **4a** could be assigned to be *R* and the absolute configuration of **4j** could be assigned to be *S*.[4d,e]



Scheme 4. Selective oxidation to diverse enantiomerically enriched 2-substituted flavanones and chromanones. General conditions: step 1, see Scheme 3. The corresponding flavanols and chromanols **2** were oxidized by reaction with PCC (3 equiv) at room temperature in CH_2Cl_2 for 10 min; e.r. was determined by HPLC on a chiral stationary phase; yields pertain to isolated product.

The presented reaction involves the hydrogenation of two double bonds, a C=C and C=O bond. A stepwise hydrogenation reaction, where the partially reduced substrate dissociates from the catalyst after the first hydrogenation step, could proceed via intermediates **A** or **B** (Scheme 5).



Scheme 5. Possible pathways for the hydrogenation of chromones.

Alternatively, a pathway in which the partially reduced substrate stays coordinated to the ruthenium center until both hydrogenation steps are completed would directly lead to the product.

To gain insight into the reaction process, a series of control experiments were conducted. First we examined the kinetics of the hydrogenation of 2-methylchromone (**1a**). The reactions were stopped at different times (0.5, 1, 1.5, 3, 6, 9, 24 h), and the reaction mixture was analyzed by ^{1}H NMR spectroscopy. We found that the reaction is quite fast (96% conversion after 3 h).[12] During the reaction, we never detected the corresponding intermediate **A** or intermediate **B**. Since it seems that these intermediates do not react faster than the starting material,[12] the involvement of the free intermediates as the main pathway is rather unlikely. Instead, the formation of a metal-bound species, such as a ruthenium enolate resulting from conjugate addition of a ruthenium hydride species to the substrate, seems more likely.[13]

In conclusion, we have developed the asymmetric hydrogenation of 2-substituted flavones and chromones leading to the formation of enantiomerically enriched flavanones, flavanols, chromanones, and chromanols using a chiral ruthenium–NHC complex. Further studies focusing on catalyst characterization, mechanistic aspects of this reaction, and hydrogenation of other challenging substrates are ongoing.

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