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Rh(II)-Cp*–TsDPEN catalyzed aqueous asymmetric transfer hydrogenation of chromenones into saturated alcohol: C=C and C=O reduction in one step

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ABSTRACT

As an efficient catalyst for asymmetric transfer hydrogenation reaction (ATH reaction) of α,β-unsaturated ketones, Rh-Cp*–TsDPEN (Cp* = 1,2,3,4,5-pentamethylcyclopenta-1,3-diene, TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenyl- ethylenediamine) shows high chemoselectivity on C=O and C=C reduction. In our method, both C=O and C=C bonds in a variety of chromenone derivatives were reduced efficiently in aqueous media, resulting in at least 98% ee and up to 99% yields in a convenient way without further purification. The product was a useful intermediate for deriving chiral chroman-4-amine, which was reported as an effective agent against hypotension and inflammatory pain by inhibiting human bradykinin B1 receptor.

Noyori type catalyst, such as Rh-Cp*–TsDPEN complex (Cp* = 1,2,3,4,5-pentamethylcyclo-penta-1,3-diene, TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenyl-ethylenediamine), is of crucial importance on ketones' ATH reaction (asymmetric transfer hydrogenation reaction). It has shown powerful reactivity as well as excellent stereo-control in many fields.[1] Moreover, it exhibits highly chemoselectivity for the C=O functional group in ATH reaction of α,β-unsaturated ketones in the organic phase.[2,3] However, the chemoselectivity of those types of catalyst would be switched from C=O to C=C bonds in the transfer hydrogenation if the solution was replaced with water.[4] In that case, as shown in our earlier study, saturated alcohol with high ee value was detected when the substrate was chalcone, which means both C=C and C=O double bonds have been reduced together.[4a] When the substrate was benzylidene acetone, which reacted with excessive HCOONa as a hydrogen source, similar chemoselectivity was observed. Besides, $[Rh\text{-}Cp^*Cl_2]_2$ was proved to be the most efficient metal source to prepare such saturated alcohol, which affords 81% conversion.[4b,c]

On the other hand, it was reported that compounds with the structure of chroman-4-amines (**4**) were effectively against hypotension and inflammatory pain as a selective antagonist of bradykinin B1 receptors.[5] The chroman-4-amines (**4**) could be easily prepared from chiral chroman-4-ol (**3**)[5,6a] by CBS,[5,6] AH,[7] or ATH[1b,8] reaction (Fig. 1). Obviously, if easy-obtained chromenone (**1**) could be reduced directly, it would be more convenient to synthesize chiral chroman-4-ol (**3**). Thus, we proposed that as a special type of α,β-unsaturated ketones, chromenone (**1**) could be reduced to chiral chroman-4-ol (**3**) in water directly catalyzed by Rh-Cp*Cl–TsDPEN.[9]

We selected chromenone (**1a**) to be the template substrate, as outlined in Table 1. For the composition of hydrogen source was proved to be of crucial effect on the activity of ATH reaction in water,[4c,10] the change of composition was initially tested at 30 °C (entries 1–4). It was clearly suggested that HCOONa with a small amount of HCOOH led to a better result (entry 2) than without HCOOH addition (entry 1). Nevertheless, the reaction with pure

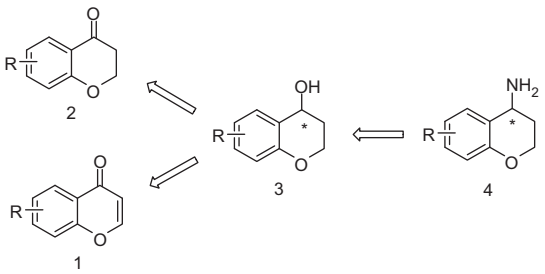

Figure 1. Preparation of chroman-4-amines (**4**) from chroman-4-ones (**2**) or chromenone (**1**).

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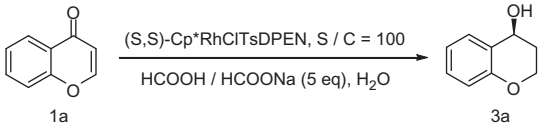
Table 1
Optimizing conditions for (*S*, *S*)-Cp*RhClTsDPEN catalyzed ATH reaction in water [a]



1a 3a

Entry	HCOOH:HCOONa	Temp (°C)	Time (h)	Conversion[b] (%)	ee[c] (%)
1	0:1	30	3	13	99
2	3:20	30	3	27	99
3	5:20	30	3	9	99
4	1:0	30	3	ND	–
5	3:20	40	3	89	99
6	4:20	40	3	93	99
7	5:20	40	3	66	99
8	2:20	60	1	80	99
9	3:20	60	1	91	99
10	4:20	60	1	93	99
11	5:20	60	1	89	99

[a] The reaction was performed with 0.0016 mmol of Cp*RhClTsDPEN, 0.16 mmol of **1a** and 0.8 mmol of HCOONa and several equivalents of HCOOH (as mentioned in table above) in 1 ml of water under argon atmosphere.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC in chiral AS column.

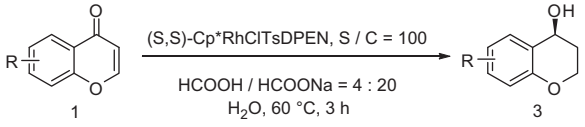
HCOOH didnot work (entry 4). When the temperature was increased to 40 °C, the conversion value elevated significantly without any decrease in ee value (entries 5–7), and the most satisfactory result was achieved by adding 1 equiv HCOOH, which yield 93% conversion. With the temperature increment, the reaction activity was increased as well (entries 8–11). Therefore, the most suitable condition should be stirring at 60 °C with the hydrogen source composed of 5 equiv HCOONa and 0.8 equiv HCOOH. This reaction condition will lead to 93% conversion and 99% ee in only 1 h, and the amount of chroman-4-ones was barely detectable.

With the best condition in hand, substrate scope was performed subsequently, as shown in Table 2. Similar to template substrate (**1a**), chromenone derivatives with electron-withdrawing substituents in benzyl ring performed perfectly on both stereo selectivity and reactivity. At least 92% isolated yield could be achieved except for **1c**.[11] Although, chromenone derivatives with electron accepter substituents also showed high ee value, the activity declined substantially. When the substituent was methyl group, only an intermediate yield was obtained (entries 8 and 11). Furthermore, fewer products were obtained when the stronger electron-donating methoxy was introduced (entries 9 and 12). Only trace amount of chroman-4-one (**2**) would be present in all the products mentioned above.[12] Pure products could be obtained by extracting the substrate-product mixture with alkaline to remove the substrate directly. It was unexpected that substrates with methyl or phenyl substitution in 2-position did not have any reactivity (entries 13 and 14).

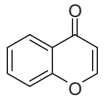
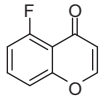
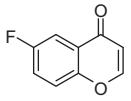
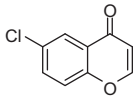
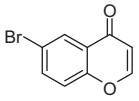
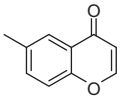
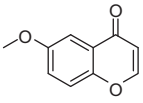
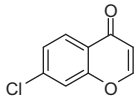
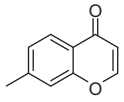
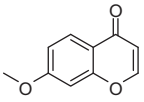
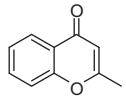
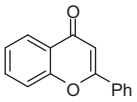
In order to explore the potential of the current catalyst system, amplification of this reaction was carried out. With 6.8 mmol of **1a** as the starting material, the reaction time was extended to 6 h in the best condition, and there was no significant decline on the reactivity and stereoselectivity (Scheme 1). After treated with alkaline, the product could be acquired with 96% isolated yield and 99% ee value.

In conclusion, a new method to prepare a series of chiral chroman-4-ol derivatives catalyzed by Rh-Cp*–TsDPEN complex was discovered. The reaction was conducted at 60 °C with excessive HCOONa and HCOOH as hydrogen source in water, and both C=C and C=O double bonds of chromenone derivatives were completely reduced in one step with at least 98% ee and up to 99% yield. In addition, the product could be obtained with a convenient procedure by adding alkaline directly. At last, the reaction was

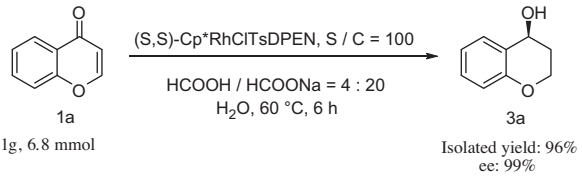
Table 2
Substances scope for (*S*, *S*)-Cp*RhClTsDPEN catalyzed ATH reaction in water[a]



1 3

Entry	Substance	Isolated yield[b] (%)	ee[c] (%)
1	**1a** 	99	99
2	**1b** 	98	99
3	**1c** 	23[11]	99
4	**1d** 	92	99
5	**1e** 	99	99
8	**1f** 	51	99
9	**1g** 	28	98
10	**1h** 	99	99
11	**1i** 	55	99
12	**1j** 	29	99
13	**1l** 	ND	–
14	**1m** 	ND	–

[a] The reaction was performed with 0.0016 mmol of Cp*RhClTsDPEN, 0.16 mmol of **1**, 0.8 mmol of HCOONa and 0.16 mmol of HCOOH in 1 ml of water at 60 °C for 3 h under argon atmosphere.
[b] The crude product was treated by ice cooled 2 N KOH solution, stirred at 10 °C for 0.5 h, extracted with CH_2Cl_2 and evaporated to afford the product.
[c] Determined by HPLC in chiral AS or OD column.



Scheme 1. The ATH reaction of **1a**–**3a** on Gram-Scale.

amplified to gram-scale, which could be utilized in asymmetric synthesis in the future.

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11. We proposed that the low conversion value might be lead by the solubility of compound **1c**.
12. The trace amount of compound **2** could be detected by HPLC technology due to its strong UV absorption, although it could not be detected by ^{1}H NMR or TLC analysis.