Rhodium-Catalyzed Asymmetric Transfer Hydrogenation/Dynamic Kinetic Resolution of 3-Benzylidene-Chromanones

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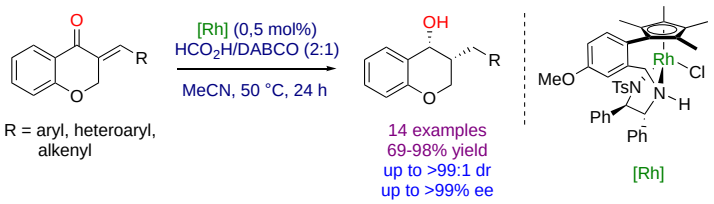
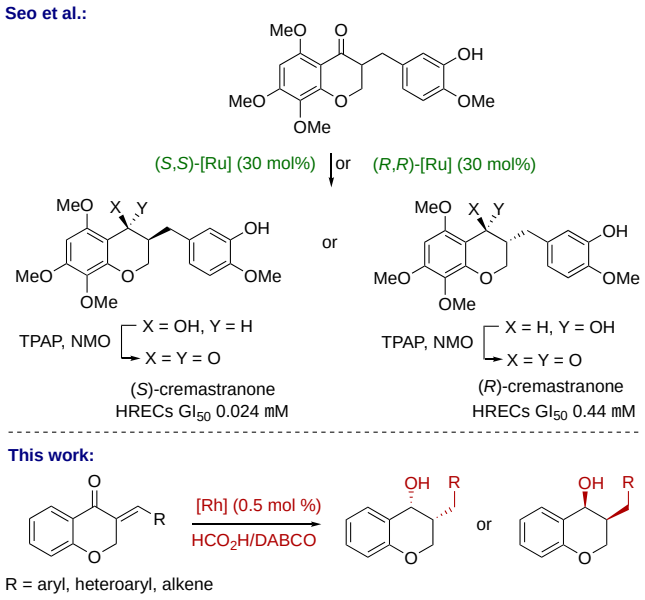
Supporting Information Placeholder



ABSTRACT: A straightforward access to enantiomerically enriched *cis*-3-benzyl-chromanols from (*E*)-3-benzylidene-chromanones was developed through Rh-catalyzed asymmetric transfer hydrogenation. This transformation allowed the reduction of both the C=C and C=O bonds and the formation of two stereocenters in high yields with excellent levels of diastereo- and enantioselectivities (up to >99:1 dr, up to >99% ee) in a single step through a dynamic kinetic resolution process using a low catalyst loading and HCO_2H/DABCO as the hydrogen source.

Homoisoflavonoids are a widespread family of molecules, naturally occurring in plants, which possess a promising set of biological activities.[1] Among those, antioxidant, anti-inflammatory, antitumoral, antiviral, antibacterial and protective vascular actions can be cited as potential therapeutic indications.[2] The 3-benzyl-chromanol substructure is present in several molecules, for example CP-105,696, which possess a selective and potent LTB_4 receptor-inhibiting ability.[3] LTB_4 is a chemoattractant for granulocytes and is involved in several inflammatory diseases such as rheumatoid arthritis or asthma. An efficient and straightforward route to access enantiomerically enriched 3-benzyl-chromanols is thus highly desirable. In this context, Koch *et al.* reported the synthesis of an enantiomerically pure 3-benzyl-chromanol starting from the ketone precursor using a chemical resolution, after $NaBH_4$ reduction, esterification with *t*-Boc-L-tryptophan and hydrolysis of the resulting ester.[4] Seo et al. later devised an asymmetric synthesis of cremastranone by using an asymmetric transfer hydrogenation (ATH) coupled with a dynamic kinetic resolution (DKR) of a 5,6,7-substituted homoisoflavanone catalyzed by Noyori's ruthenium complex [RuCl(*p*-cymene){(*S*,*S*)-Ts-DPEN}] or [RuCl(*p*-cymene){(*R*,*R*)-Ts-DPEN}], followed by TPAP oxidation of the resulting enantiomerically enriched alcohol.[5] The ATH reaction proceeded using a 3:1 mixture of DBU/HCO_2H as the hydrogen source, and a catalyst loading of 30 mol% to achieve full conversion. Subsequent oxidation of the alcohol with TPAP gave the desired (*R*) and (*S*)-cremastranone without racemization, allowing confirmation of the absolute configuration of the natural product as (*R*) and showing that the anti-angiogenic effect of the (*S*)-isomer was superior to the natural (*R*)-form.

Scheme 1. Catalytic asymmetric reduction of 3-substituted chromanones



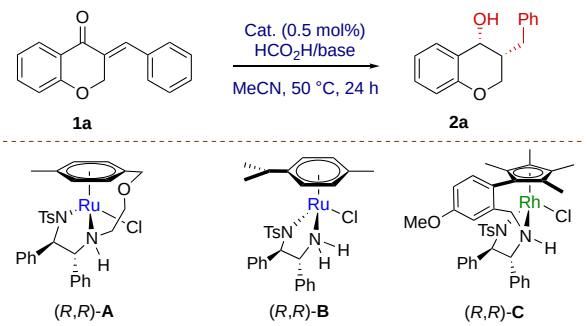
The authors used the same strategy for the total synthesis of several 5,7,8-trioxygenated chroman-4-ones and homoisoflavonoids.[6]

In the context of our ongoing studies directed toward the development of efficient methods for the asymmetric reduction of functionalized ketones[7] and in order to access a wide range of 3-benzyl-chromanol derivatives, we report herein the first rhodium-catalyzed asymmetric transfer hydrogenation of

3-benzylidene-chromanones that efficiently reduces both the C=C and C=O bonds in a single synthetic step and provides in good yields the targeted molecules with excellent levels of diastereo- and enantioselectivity through a dynamic kinetic resolution process (DKR).[8]

To investigate the proposed ATH-DKR, racemic (*E*)-3-benzylidene-chromanone **1a**[9,10] was subjected to the asymmetric reduction using several organometallic catalysts in acetonitrile at 50 °C for 24 h (Table 1).

Table 1. Catalyst screening for the ATH of 1a[a]



entry	cat.	HCO_2H/Base	yield of 2a[b] (%)	dr[c]	ee[d] (%)
1	(*R*,*R*)-**A**	HCO_2H/Et_3N	84	77:23	>99
2	(*R*,*R*)-**B**	HCO_2H/Et_3N	92	92:8	95
3	(*R*,*R*)-**C**	HCO_2H/Et_3N	91	97:3	99
4	(*R*,*R*)-**B**	HCO_2H/DBU	96	93:7	98
5	(*R*,*R*)-**C**	HCO_2H/DBU	95	97:3	>99

[a]Conditions: **1a** (0.79 mmol), cat. (0.5 mol%), 5 equiv of HCO_2H/Et_3N (5:2) or HCO_2H/DBU (2:1), MeCN (1.5 mL), 50 °C. [b]Isolated yield, complete conversion in all cases. [c]Determined by ^1H NMR of the crude product after the ATH reaction. [d]ee for the *cis* product determined by SFC analysis.

The HCO_2H/Et_3N (5:2) azeotropic mixture (5 equiv) was first used as the hydrogen source in the presence of 0.5 mol% of rhodium or ruthenium complexes (Table 1, entries 1-3). These conditions led to a full conversion with all the tested complexes. The ATH using oxo-tethered ruthenium catalyst (*R*,*R*)-**A**[11] occurred with a modest diastereomeric ratio of 77:23 in favor of the *cis* alcohol **2a**, which was obtained in 84% yield and >99% ee (Table 1, entry 1). With the [RuCl(*p*-cymene){(*R*,*R*)-Ts-DPEN}] complex (*R*,*R*)-**B**,[12] a high yield (92%) and high levels of diastereo- and enantioinductions were observed (Table 1, entry 2, 92:8 dr, 95% ee). We were delighted to find that the home made (*R*,*R*)-**C**[12] containing an (*R*,*R*)-TsDPEN ligand tethered to the ancillary η^5-arene ligand outperformed the previous catalysts by yielding a diastereomeric ratio of 97:3 and 99% ee (Table 1, entry 3). We next chose to screen a variety of bases and replaced triethylamine with DBU in the hydrogen source mixture. The use of a HCO_2H/DBU (2:1) combination pleasingly allowed a slight increase of the yield of **2a** with both (*R*,*R*)-**B** and (*R*,*R*)-**C**, the latter still giving the best stereoselectivities (Table 1, entries 4 and 5). Based on this encouraging series of results, the rhodium complex (*R*,*R*)-**C** was chosen as the catalyst for this study.

The investigations continued with the screening of the solvent, the catalyst loading (S/C) and the nature of the hydrogen donor (Table 2). Several solvents such as CH_3CN, CH_2Cl_2, THF, toluene, AcOEt, *i*-PrOH, and MeOH performed well (Table 2, entries 1-7). High yields of 84-95% were obtained in these solvents with diastereomeric ratios ranging from 90:10 to 97:3 and enantioselectivities of 99% to >99% ee, with acetonitrile giving the best results.

Table 2. Optimization of the reaction conditions[a]

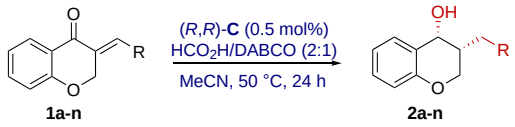
entry	solvent	hydrogen donor	yield[b] (%)	dr[c]	ee[d] (%)
1	CH_3CN	HCO_2H/DBU (2:1)	95	97:3	>99
2	CH_2Cl_2	HCO_2H/DBU (2:1)	94	92:8	99
3	THF	HCO_2H/DBU (2:1)	92	96:4	>99
4	toluene	HCO_2H/DBU (2:1)	84	96:4	>99
5	AcOEt	HCO_2H/DBU (2:1)	87	97:3	>99
6	*i*-PrOH	HCO_2H/DBU (2:1)	88	90:10	>99
7	MeOH	HCO_2H/DBU (2:1)	95	93:7	99
8[e]	MeCN	HCO_2H/DBU (2:1)	94	96:4	>99
9[f]	MeCN	HCO_2H/DBU (2:1)	43	97:3	>99
10	MeCN	HCO_2NH_4	49	92:8	98
11[g]	MeCN	$(HCO_2)_2Ca$	63	74:26	89
12[h]	MeCN	*i*-PrOH/KOH	–	–	–
13	MeCN	HCO_2H/DABCO (2:1)	96	99:1	>99

[a]Conditions: **1a** (0.79 mmol), (*R*,*R*)-**C** (0.5 mol%), hydrogen donor (5 equiv), solvent (1.5 mL), 50 °C, 24 h. [b]Isolated yield of **2a**. [c]Determined by ^1H NMR of the crude product after the ATH reaction. [d]ee for the *cis* product determined by SFC analysis. [e]0.25 mol% of (*R*,*R*)-**C** were used. [f]0.1 mol% of (*R*,*R*)-**C** were used. [g]0.1 mL of water were added. [h]3 equiv of *i*-PrOH/KOH were used.

Next, the S/C ratio was progressively lowered (Table 2, entries 8 and 9). Increasing the S/C to 400 did not affect the outcome of the ATH reaction. However, using a S/C of 1000 had a detrimental effect on the yield, which dropped to 43%. To complete the optimization of the reaction parameters, other hydrogen sources were examined. Formate salts such as HCO_2NH_4 and $(HCO_2)_2Ca$ led to lower yields with a significant unfavorable impact on the stereoselectivity in the latter case (Table 2, entries 10-11). Whereas using potassium hydroxide in isopropanol failed to afford any conversion (Table 2, entry 12), the hindered 1,4-diazabicyclo[2.2.2]octane (DABCO) gave excellent results allowing the diastereoselectivity to reach 99:1 dr while maintaining the enantioselectivity at >99% ee (Table 2, entry 13). From this survey, the optimized conditions were set as follows: (*R*,*R*)-**C** (0.5 mol%) as the precatalyst, HCO_2H/DABCO (2:1) (5 equiv) as the hydrogen source in CH_3CN solvent at 50 °C.

Having identified an effective stereoselective method to set the vicinal stereocenters and being amenable to a dynamic kinetic resolution process (DKR), we explored the scope and limitations of the asymmetric reduction on a series of 3-benzylidene-chromanone derivatives that could be utilized in this novel DKR transformation (Table 3). Good results were obtained with a wide range of arene substitution by varying the position (*ortho*, *meta* or *para*) of the methoxy group on the aryl ring of the benzylidene moiety, and compounds **2b-2d** were formed in 92-95% yields, 99:1 dr and enantioselectivities up to >99% ee (Table 3, entries 2-4). Other 3-benzylidene-chromanone derivatives bearing either electron-donating or electron-withdrawing groups were efficiently reduced to the corresponding *cis* alcohols with good yields up to 93% and high levels of diastereo- and enantioselectivities (Table 3, entries 5-10, up to 99:1 dr, up to >99% ee).

Table 3. Substrate scope of the ATH/DKR of 1a-1n[a]



1a-n **2a-n**

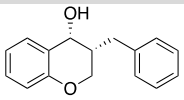
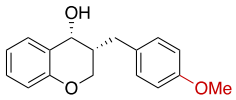
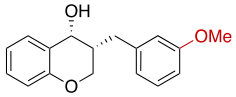
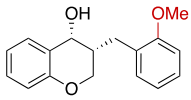
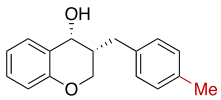
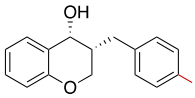
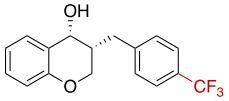
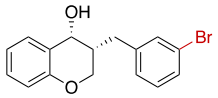
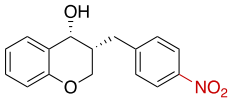
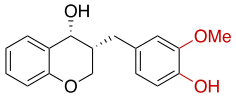
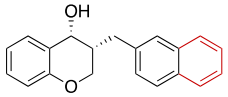
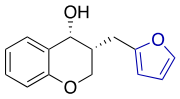
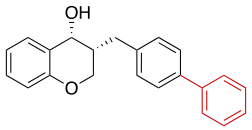
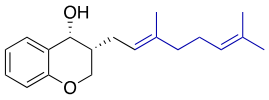
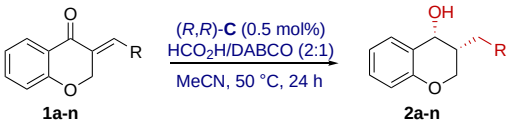
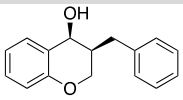
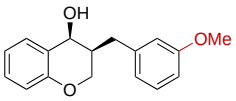
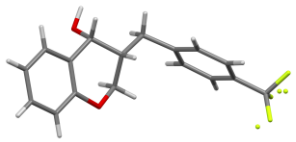
entry/ATH product **2**	Yield[b] (%)	dr[c]	ee[d] (%)
1/**2a** 	96	99:1	>99
2/**2b** 	95	99:1	>99
3/**2c** 	93	99:1	>99
4/**2d** 	92	99:1	97
5/**2e** 	93	99:1	>99
6/**2f** 	92	99:1	99
7/**2g** 	93	99:1	>99
8/**2h** 	91	99:1	>99
9/**2i** 	82	99:1	99
10/**2j** 	94	99:1	>99
11/**2k** 	95	99:1	98
12/**2l** 	77	99:1	>99
13/**2m** 	98	>99:1	99
14/**2n** 	69	94:6	>99

Table 3 (*contd.*)



1a-n **2a-n**

entry/ATH product **2**	Yield[b] (%)	dr[c]	ee[d] (%)
15[e]/**2o** 	96	99:1	>99
16[e]/**2p** 	91	99:1	>99



X-ray crystallography of **2g**. Displacement ellipsoids are shown at the 30% probability level.

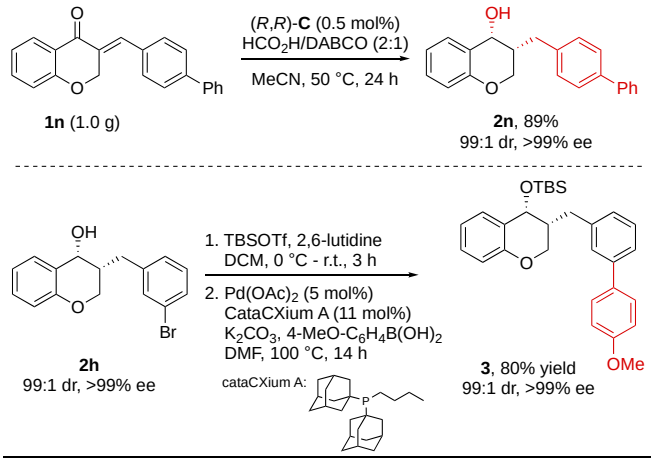
[a]Conditions: **1a-n** (0.79 mmol), (*R*,*R*)-**C** (0.5 mol%), 5 equiv of HCO_2H/DABCO (2:1), MeCN (1.5 mL). [b]Isolated yield, complete conversion in all cases. [c]Determined by ^1H NMR of the crude product after the ATH reaction. [d]ee for the *cis* product determined by SFC analysis. [e]The ATH reaction was performed with complex (*S*,*S*)-**C** under otherwise identical conditions.

Interestingly, a bulky substituent such as a naphthyl group (Table 3, entry 11) as well as a heteroaryl substituent such as a furyl subunit or biphenyl substituents (Table 3, entry 12 and 13 respectively) were well-tolerated. Importantly, the reaction was not limited to arylchromanone derivatives and an alkenyl substituted chromanone was also accommodated in this transformation (Table 3, entry 14). In this case, the reduction proved to be chemoselective of the C=C bond located next to the carbonyl group yielding the corresponding *cis*-chromanol in good yield (69%), good diastereoinduction (94:6 dr) and excellent enantiocontrol (>99% ee).

The absolute configuration of compound **2g** was unambiguously determined as (*R*,*R*) by X-ray crystallographic analysis, and by analogy we conjectured that the remainder of the ATH products followed the same trend. In addition, the (*S*,*S*)-alcohols **2o** and **2p** could be readily prepared as well by using the (*S*,*S*)-isomer of the rhodium complex **C** instead of the (*R*,*R*)-enantiomer. In both cases the reduced compounds were obtained with results comparable to those obtained for the parent alcohols **2a** and **2b**, respectively (Table 3, entries 15-16 vs entries 1-2).

The utility of the developed reaction was illustrated by its performance on gram-scale. Compound **1n** was subjected to the ATH-DKR under the same reaction conditions to provide **2n** in 89% yield, 99:1 dr and >99% ee (Scheme 2). Furthermore, compound **2h** was post-functionalized into **4** in 80% yield and no loss of dia- and enantioselectivity by protecting the alcohol group with a *tert*-butyl-*di*-methyl silane group followed by a Suzuki-Miyaura cross-coupling by using $Pd(OAc)_2$, cataCXium A as ligand, K_2CO_3 as a base, 4-methoxyphenylboronic acid and DMF as solvent.

Scheme 2. Post-functionalization and Scale-Up



In summary, the practical rhodium-catalyzed asymmetric transfer hydrogenation of 3-benzylidene chromanones allows reduction of two double bonds in a single step in a stereo-controlled manner. The unique combination of Rh(III) complex developed in the group and formic acid/DABCO (2:1) as hydrogen source enables at low catalyst loading under mild conditions, the facile reductive dynamic kinetic resolution of 3-benzylidene chromanones to access the corresponding *cis*-3-benzyl chromanols in high yields and excellent stereoselectivities (up to >99:1 dr, up to >99% ee). This efficient and straightforward catalytic route provides access to synthetically useful chromanol derivatives and valuable chroman pharmacophores as well and tolerates a broad range of functionalities.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compound characterization data, NMR spectra and SFC data (PDF)

CCDC 2048735 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033

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Notes

The authors declare no competing financial interest.

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