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

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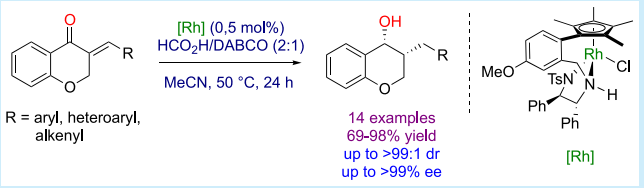
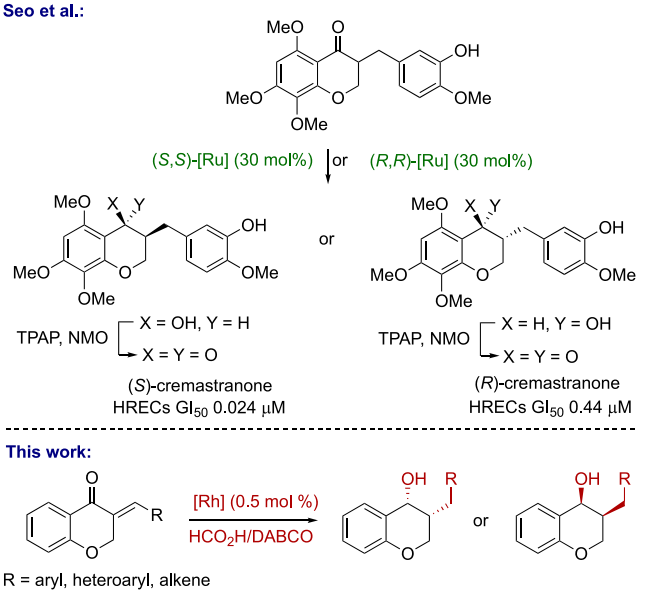
ABSTRACT: Straightforward access to enantiomerically enriched *cis*-3-benzyl-chromanols from (*E*)-3-benzylidene-chromanones was developed through Rh-catalyzed asymmetric transfer hydrogenation. This transformation allowed the reduction of both the C═C and C═O bonds and the formation of two stereocenters 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, that possess a promising set of biological activities.[1] Among them, 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, that 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 and 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 to 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 tetrapropylammonium perruthenate (TPAP) oxidation of the resulting enantiomerically enriched alcohol (Scheme 1).[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 antiangiogenic effect of the (*S*) isomer was superior to the natural (*R*) form.

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

Scheme 1. Catalytic Asymmetric Reduction of Three-Substituted Chromanones



In the context of our ongoing studies directed toward the development of efficient methods for the asymmetric reduction of functionalized ketones[7] and to access a wide range of 3-

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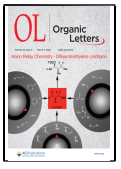

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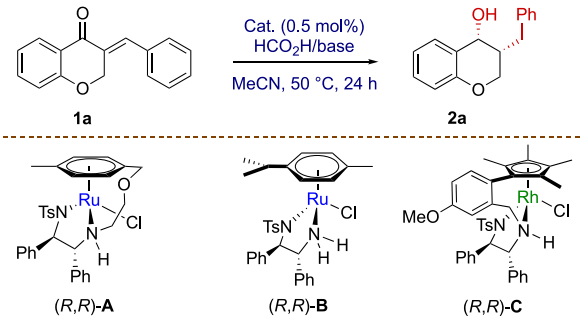
benzyl-chromanol derivatives, we report herein the first rhodium-catalyzed ATH of 3-benzylidene-chromanones that efficiently reduces both the C=C and C=O bonds in a single synthetic step and provides in good yields the targeted molecules with excellent levels of diastereo- and enantioselectivity through a DKR process.[8]

To investigate the proposed ATH/DKR, racemic (*E*)-3-benzylidene-chromanone **1a**[9,10] was subjected to 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 supercritical fluid chromatography (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 of the tested complexes. The ATH using an 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 with >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 homemade (*R*,*R*)-**C**[13] 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 with 99% ee (Table 1, entry 3). We next chose to screen a variety of bases and replaced triethylamine with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the hydrogen source mixture. The use of a HCO_2H/DBU (2:1) combination pleasingly allowed a slight increase in 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). On the basis of 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** was used. [f]0.1 mol % of (*R*,*R*)-**C** was used. [g]0.1 mL of water was added. [h]3 equiv of *i*-PrOH/KOH was used.

Next, the S/C ratio was progressively increased (Table 2, entries 8 and 9). Increasing the S/C to 400 did not affect the outcome of the ATH reaction. However, using an 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 and 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 and 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 DKR process, 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 with 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 in good yields up to 93% with high levels of diastereo- and enantioselectivities (Table 3, entries 5−10, up to 99:1 dr, up to >99% ee).

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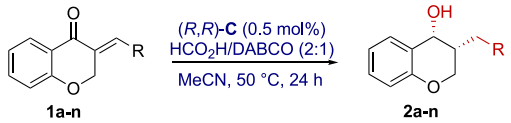
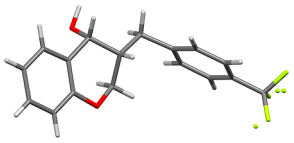
Org. Lett. 2021, 23, 1621−1625

Table 3. Substrate Scope of the ATH/DKR of 1a−1n[a]



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
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−1n** (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]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) and a heteroaryl substituent such as a furyl subunit or biphenyl substituents (Table 3, entries 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%) with 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 and 16 vs entries 1 and 2).

The utility of the developed reaction was illustrated by its performance on the gram scale. Compound **1n** was subjected to the ATH/DKR under the same reaction conditions to provide **2n** in 89% yield with 99:1 dr and >99% ee (Scheme 2). Furthermore, compound **2h** was postfunctionalized into **4** in

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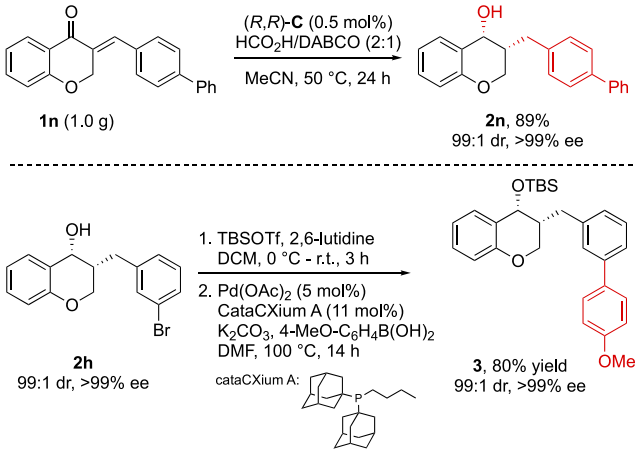
Org. Lett. 2021, 23, 1621−1625

Scheme 2. Post-Functionalization and Scale-Up



80% yield with no loss of diastereo- or 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 the ligand, K_2CO_3 as a base, 4-methoxyphenylboronic acid, and dimethylformamide (DMF) as the solvent.

In summary, the practical rhodium-catalyzed ATH of 3-benzylidene chromanones allows the reduction of two double bonds in a single step in a stereocontrolled manner. The unique combination of the Rh(III) complex developed in the group and formic acid/DABCO (2:1) as a hydrogen source enables at low catalyst loading under mild conditions the facile reductive DKR of 3-benzylidene chromanones to access the corresponding *cis*-3-benzyl chromanols in high yields with 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 at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00047.

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

Accession Codes

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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