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Access to Enantioenriched β -Hydroxy *gem*-Difluorinated Heterocyclic and Acyclic Derivatives through Rh(III)-Catalyzed Asymmetric Transfer Hydrogenation

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Abstract. We report here a rapid, efficient, and easy to handle process to access a variety of enantioenriched α -*gem*-difluorinated alcohols. A Rh(III)-catalyzed asymmetric transfer hydrogenation method was developed in yields up to 98% and enantiomeric excesses up to >99%. The reduction proceeds under mild conditions with a range of difluorinated molecules including 3,3-difluorochromanone, 3,3-difluorothiochromanone, 3,3-difluoro-dihydroquinolinone and α -difluorinated β -ketosulfone derivatives to efficiently provide the desired enantioenriched difluorinated alcohols which are valuable novel fluorinated building blocks.

Keywords: Asymmetric transfer hydrogenation; Enantioselectivity; Homogeneous catalysis; Heterocycles; Transition metals

Because of the distinctive characteristics of fluorine, the targeted incorporation of fluorine atom(s) or fluorine-containing groups into organic compounds frequently results in profound changes to their stability, hydrophobicity, accessibility to biological systems, and biological potency influencing the administration and processing of pharmaceuticals in the body.^[1] Consequently, fluorine is emphasized as the second most commonly employed heteroelement,^[2] following nitrogen, in research oriented toward the life sciences.^[3] More specifically, the geminal difluoromethylated moiety can function as a bioisostere of ether oxygen,^[4] leading to potential conformational shifts.^[5] Additionally, in proximity to oxygen, two fluorine atoms significantly alter the fundamental properties of basicity and hydrogen bonding in alcohols.^[6] Because of its significant interest in bioisosteric design,^[7] the CF₂ moiety has

the potential to influence physicochemical and pharmacological characteristics of a compound (Figure 1).^[8]

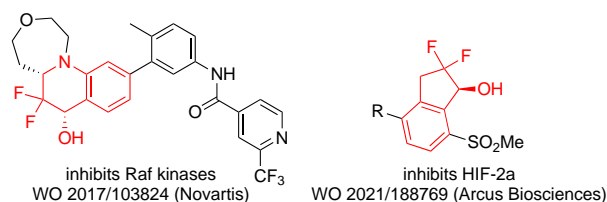


Figure 1. Examples of chiral bioactive β -hydroxy *gem*-difluorinated molecules.

Considering the significant characteristics of the pattern outlined earlier, and in line with our ongoing efforts focused on generating valuable enantioenriched fluorinated compounds,^[9] we hereby report the synthesis of a new range of β -hydroxy *gem*-difluorinated heterocyclic and non-cyclic derivatives through an asymmetric transfer hydrogenation (ATH)^[10] process. Our investigations started with the preparation of a variety of α -*gem*-difluorinated ketones **3a-3q** including 3,3-difluorochromanones **3a-3i** bearing diverse electron-donating or electron-withdrawing groups on the aryl ring as well as 3,3-difluorothiochromanone **3j**, 3,3-difluoro-dihydroquinolinones **3k-3o** and α -difluorinated β -ketosulfone **3p-3q** derivatives. For the 3,3-difluorochromanone series, the products **3a-3i** were synthesized through a two-step sequence involving first the α -monofluorination of the ketones **1a-1i** using Selectfluor in the presence of H₂SO₄ in MeOH to deliver **2a-2i** in 32-98% yield. The second fluorination reaction was performed on the corresponding silyl enol ether to afford the desired products **3a-3i** in 61 to 96% yield (Figure 2a).^[11] The

3,3-difluorothiochromanone derivative **3j** was prepared in 64% yield by using NFSI as the fluorinating agent through sequential fluorination of thiochroman 4-one **1j** with LiHMDS as a base.^[12] On the other hand, the 3,3-difluoro-dihydroquinolinone derivatives **3k-3o** were obtained in a single step in 45-61% yield using 6 equivalents of NaH and 4 equivalents of NFSI.^[13] Finally, α -difluorinated phenylsulfonyl derivatives **3p** and **3q** were formed by sequential fluorination of the β -keto sulfones **1p-1q**, using sodium carbonate and Selectfluor at room temperature in 51% (**3p**, R = Me) and 86% (**3q**, R = Ph) yield over 2 steps.^[14]

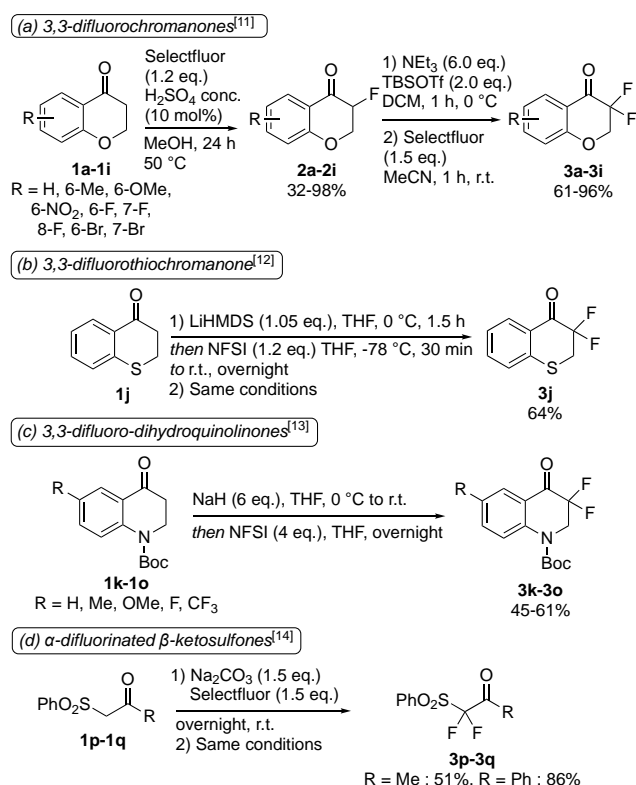


Figure 2. Synthesis of *gem*-difluorinated ketones.

Having those substrates in hand, we next investigated the enantioselective reduction of 3,3-difluorochroman-4-one **3a** as a model substrate by evaluating the catalytic properties of a series of commercially available ruthenium catalysts such as (*R,R*)-**A**, (*R,R*)-**C**, (*R,R*)-**D** or a Rh-based catalyst (*R,R*)-**B** previously developed in our group,^[15] using dichloromethane as a solvent at a concentration of 0.3 M and a mixture of formic acid/triethylamine (5:2) as the hydrogen donor at 30 °C (Table, entries 1-4). All the screened complexes led to high enantioselectivities (>99% ee). However, because the rhodium-based complex allowed a full conversion with a reaction rate much shorter than the other catalysts, the optimization of the reaction parameters was performed with (*R,R*)-**B**. Thus, switching from dichloromethane to 2-MeTHF as a solvent or

decreasing the catalyst loading to 0.5 mol% showed no significant impact on the yield and ee although the kinetics of the reaction was slightly improved (Table, entries 5 and 6). Using the ruthenium complexes (*S,S*)-**E** and (*R,R*)-**F** under the above conditions failed to afford complete conversion even with prolonged reaction time (Table, entries 7 and 8).

Table. Optimization of the reaction parameters^[a]

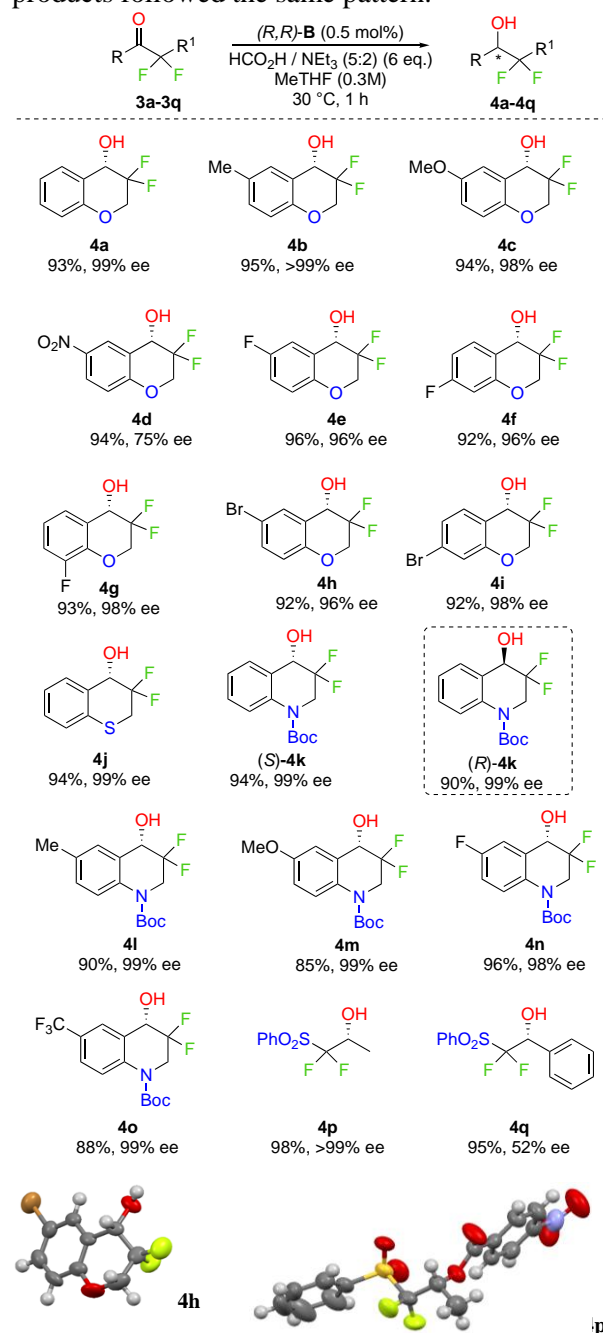
Entry	Cat. mol%	Solvent	t (h)	Yield ^[b] (%)	ee ^[c] (%)
1	(<i>R,R</i>)- A	DCM	5	94	>99
2	(<i>R,R</i>)- B	DCM	2	97	>99
3	(<i>R,R</i>)- C	DCM	6	94	>99
4	(<i>R,R</i>)- D	DCM	4	94	>99
5	(<i>R,R</i>)- B	MeTHF	1.5	95	99
6	(<i>R,R</i>)- B	MeTHF	1	94	99
7	(<i>S,S</i>)- E	MeTHF	70	91 ^[d]	95
8	(<i>R,R</i>)- F	MeTHF	70	18 ^[d]	31
9 ^[e]	(<i>R,R</i>)- B	MeTHF	1	93	99
10 ^[f]	(<i>R,R</i>)- B	MeTHF	1	90	99
11 ^[g]	(<i>R,R</i>)- B	MeTHF	2	92	97
12	(<i>R,R</i>)- B	neat	2	91	96
13	(<i>R,R</i>)- B	MeCN	1	90	98
14	(<i>R,R</i>)- B	AcOEt	1	90	99

[a] Reaction conditions: **3a** (0.43 mmol, 80 mg), Cat. (X mol%), HCO₂H/NEt₃ (5:2) (218 μ L, 6.0 eq.), solvent (0.3 mol/L), 30 °C, t (h), under argon. Full conversion was observed except where indicated. [b] Yields were obtained after filtration on a pad of silica gel. [c] Enantiomeric excess was determined by SFC analysis with a chiral stationary phase. [d] Conversion is reported. [e] Open flask. [f] HCO₂H/NEt₃ (1:1). [g] A concentration of 1 mol/L was used.

Interestingly, the reaction could be performed in an open flask with no effect on the catalytic performances as compared to those observed for the

reaction carried out under argon atmosphere (Table, entries 9 vs 6). Varying the ratio of the formic acid/triethylamine mixture from 5:2 to 1:1 furnished **4a** in a slightly lower yield of 90% (Table, entry 10) whereas reducing the catalyst loading to 0.1 mol% had a detrimental impact on the enantioselectivity of the reduction either in solution or neat (97% and 96% ee, respectively, Table, entries 11 and 12). Other solvents such as acetonitrile or ethyl acetate were tested, giving similar results as 2-MeTHF in terms of reaction time, yield and enantioselectivity (Table, entries 13 and 14). However, because it is considered a greener solvent, we chose to work with 2-MeTHF and the optimized reaction conditions were set as follows: 2-MeTHF at a 0.3 M concentration, in a mixture of formic acid/triethylamine (5:2) at 30 °C for 1 hour, with the rhodium-based catalyst at a 0.5 mol% catalyst loading. To further assess the scope of the reduction with these optimized conditions in hand, we next investigated the Rh-catalyzed ATH of the α -gem-difluorinated ketones **3a-3q** (Scheme 1). Various substituted 3,3-difluorochroman-4-ones **3a-3i** were subjected to the asymmetric hydrogen transfer and successfully reduced in high yields (92-96%) and enantioinductions ranging from 75% to >99% ee. The lowest ee was observed for the ATH of substrate **3d** having the nitro electron-withdrawing group on the phenyl ring (75% ee for **4d**) whereas those bearing halogen atoms (**4e-4i**) or electron-donating groups such as a methyl or methoxy (**4b, 4c**) gave high enantioselectivities. Satisfyingly, 3,3-difluorothiochroman-4-ol **4j** was obtained in comparable yield (94%) and excellent enantioselectivity of 99% as those observed for the chroman-4-ol derivatives. The 3,3-difluorodihydroquinolinones were also submitted to the ATH under the optimized reaction conditions and delivered the corresponding alcohols **4k-4o** in high yield (85-96%) and excellent enantioselectivities (98-99%). Finally, we turned our attention to acyclic difluorinated ketones. To this end, the ATH process was applied to the 1,1-difluoro-1-(phenylsulfonyl)propan-2-one derivative **3p**, leading to **4p** with an excellent 98% yield and >99% ee but a decreased ee of 52% was observed for the reduction of the parent compound 2,2-difluoro-1-phenyl-2-(phenylsulfonyl)ethan-1-one **3q**. We hypothesized that the enantioselectivity observed for the reduction of the methyl ketone **3p** arises from a stabilizing C(sp³)-H/F interaction that leads to the (*R*)-alcohol **4p**. The lower enantioselectivity observed for the ATH of phenyl ketone **3q** could be explained by a competitive C(sp³)-H/ π interaction which would favor the (*S*)-alcohol (see Supporting Information). The absolute configuration of alcohol **4h** was unambiguously determined as (*S*) through X-ray crystallographic investigation. Based on this result,

we postulated that the remaining ATH heterocyclic products followed the same pattern.

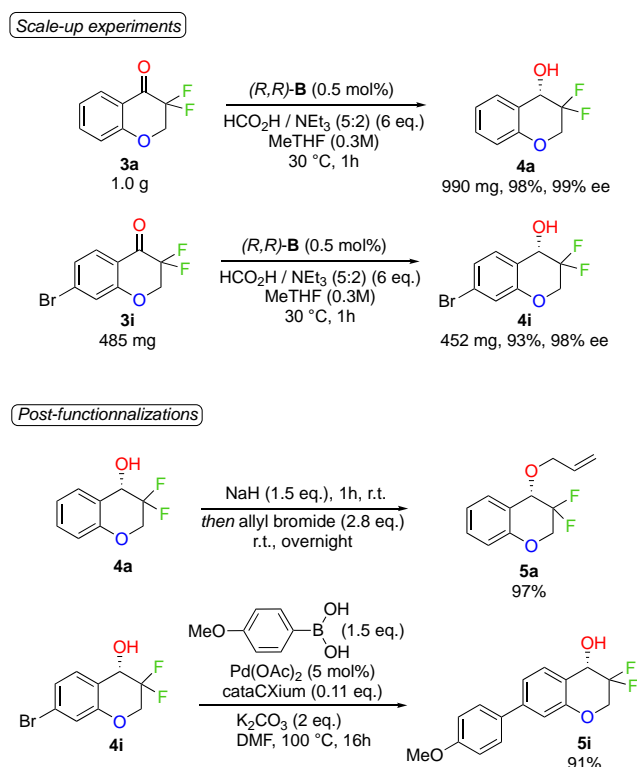


[a] Reactions conditions: **3a** (0.43 mmol, 80 mg), (R,R) -**B** (0.5 mol%, 1.65 mL of a 1 mg/mL solution in 2-MeTHF), HCO₂H/NEt₃ (5:2) (218 μ L, 6 eq.), 30 °C, 1 h, open-flask. Isolated yields were obtained after filtration on a pad of silica gel. Enantiomeric excesses were determined by SFC or HPLC analysis with a chiral stationary phase.

Scheme 1. Scope of the asymmetric transfer hydrogenation^[a]

On the other hand, the absolute configuration of the β -hydroxy sulfone **4p** was assigned through X-ray crystallographic analysis of the corresponding *p*-nitro benzoyl ester **4p'** whereas the configuration of alcohol **4q** was attributed by comparison of the

optical rotation value with reported literature data.^[16] Of note, the enantiomers of the enantioenriched β -hydroxy *gem*-difluorinated heterocyclic and acyclic compounds would be readily prepared by using the complex (*S,S*)-**B** instead of the (*R,R*)-isomer. For instance, the asymmetric reduction of **3k** using the rhodium complex (*S,S*)-**B** furnished the desired alcohol (*R*)-**4k** with similar yield and ee value as expected. The effectiveness of this asymmetric transfer hydrogenation process was supported by two scale-up experiments conducted under the defined standard conditions using 3,3-difluorochroman-4-one **3a** and 7-bromo-3,3-difluorochroman-4-one **3i** (Scheme 2). The yields observed were slightly higher (up to 98% yield) than the ones obtained on smaller scale whereas the enantioselectivities remained unchanged. Furthermore, post-functionalization on 3,3-difluorochroman-4-ol **4a** using NaH as a base and allyl bromide as the electrophile allowed the formation of the desired *O*-allylated product **5a** in an excellent yield of 97%. Additionally, post-functionalization of (*S*)-7-bromo-3,3-difluorochroman-4-ol **4i** was performed using a Suzuki–Miyaura coupling with Pd(OAc)₂, cataCXium A as a ligand, K₂CO₃ as a base, and 4-methoxyphenylboronic acid as a coupling partner. This procedure provided access to the biaryl derivative **5i**, with a yield of 91%.



Scheme 2. Post-functionalization reactions and scale-up experiments

In conclusion, we have developed a simple, robust and easy-to-handle method of rhodium-catalyzed asymmetric transfer hydrogenation for the preparation of a variety of enantiomerically enriched α -*gem*-difluorinated alcohols that are potential key building blocks. Interestingly, the reaction proceeds in an open flask, in the eco-friendly 2-MeTHF solvent at 30 °C using a low catalyst loading of 0.5 mol%, with a Rh(III) complex synthesized in our laboratory and with a mixture of formic acid/triethylamine (5:2) as the hydrogen donor source. High yields ranging from 85% to 98% alongside enantioselectivities up to >99% ee were obtained affording α -*gem*-difluorinated alcohols tolerating diverse electron-rich or electron-poor substituents in various positions on the aryl ring. Thus, Rh(III)-catalyzed ATH enables to efficiently access under mild conditions a variety of enantioenriched β -hydroxy *gem*-difluorinated heterocyclic and acyclic compounds which represent novel fluorinated building blocks of crucial importance in chemistry. Moreover, the ability of the ATH to proceed at scalable conditions without any adverse impact shows promises for future applications. Finally, the resulting compounds can act as valuable frameworks that can undergo subsequent functionalization on either the hydroxyl functional group or the halogen-bearing phenyl ring.

Experimental Section

General procedure for the asymmetric transfer hydrogenation

A round-bottom tube was charged with the corresponding *gem*-difluorinated ketone (0.43 mmol, 1.0 eq.) under air. 1.65 mL (2 μ mol, 0.005 eq.) of a solution of (*R,R*)-**B** (1 mg/mL in 2-MeTHF) was then introduced. The mixture was stirred for one minute before adding by syringe the necessary volume of formic acid/triethylamine (5:2) mixture (218 μ L, 2.61 mmol, 6.0 eq.). The reaction was stirred at 30 °C with an oil bath for 1 h and the solvent was evaporated under reduced pressure. The remaining oil was diluted in CH₂Cl₂, filtered over a short pad of silica gel and concentrated under vacuum. The enantiomeric excess was determined by SFC or HPLC analysis.

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