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Impact of the Difluoromethylene Group in the Organocatalyzed Acylative Kinetic Resolution of α,α -Difluorohydrins

Titouan Desrues, Jérémy Merad, Daniela Andrei, Jean-Marc Pons, Jean-Luc Parrain, Maurice Médebielle,* Adrien Quintard,* and Cyril Bressy*

Dedicated to Prof. Mark Lautens on the occasion of his 62nd birthday

Abstract: Due to the omnipresence of chiral organofluorine compounds in pharmaceutical, agrochemical, and material chemistry, the development of enantioselective methods for their preparation is highly desirable. In the present study, the enantioselective organocatalyzed acylation of α,α -difluorohydrins using a commercially available chiral isothiourrea is reported through a kinetic resolution (KR) process. It reveals that the difluoromethylene moiety ($C(sp^3)F_2$) can serve as a directing group through electrostatic fluorine–cation interactions, greatly improving the enantioselectivity of the KR. In this context, a broad range of fluorinated alcohols such as valuable 4,4-difluoro-1,3-diols could be synthesized with exquisite enantiocontrol (typically >99:1 er). Turning to 2,2-difluoro-1,3-diols, we also demonstrated that aromatic and fluorinated groups were mutually compatible to provide the expected enantioenriched adducts with >99:1 er.

Introduction

Fluorine chemistry represents an essential field of organic synthesis due to the omnipresence of fluorinated compounds in pharmaceuticals,^[1] agrochemicals^[2] and materials.^[3] Fluorinated groups can confer to these molecules several key physical and chemical properties by changing parameters such as conformation, polarity, pK_a , metabolic pathway, viscosity.^[4] The presence of fluorine atoms might also play a pivotal role in the recognition by enzymes as recently demonstrated by Gilmour.^[5] Due to the particular reactivity of this element, the preparation of organofluorinated compounds is less conventional than other organic functions.^[6]

Among all fluorinated scaffolds, the difluoromethylene group ($C(sp^3)F_2$) has received less attention.^[7] To date, six-FDA approved pharmaceuticals bearing a CF_2 group are known, including gemcitabine or Tafluprost (Figure 1).

In consequence, the development of methods to obtain chiral building blocks bearing a CF_2 group is highly promising. Moreover, the use of fluorinated substrates in enantioselective catalysis can, in some cases, unveil singular interactions or effects with catalytic species.^[8]

Chiral isothiourreas emerged in 2006 as a class of powerful Lewis base organocatalysts,^[9] becoming popular in several enantioselective transformations including the crucial acylation of racemic alcohols.^[10] This class of catalysts easily reacts with electrophilic centers such as carboxylic derivatives, anhydrides and activated esters. A network of non-covalent interactions (NCI) governs the selectivity in the accepted transition state described by Birman and Houk^[11] (Scheme 1):

- 1) The phenyl group prevents the access of the incoming alcohol by the lower face.
- 2) The sulfur atom interacts with a lone pair of the oxygen atom of the acyl group through a chalcogen interaction locking the rotation around the C–N bond.^[12]

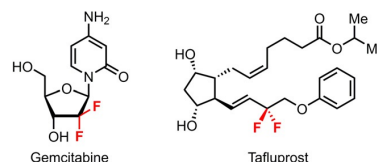
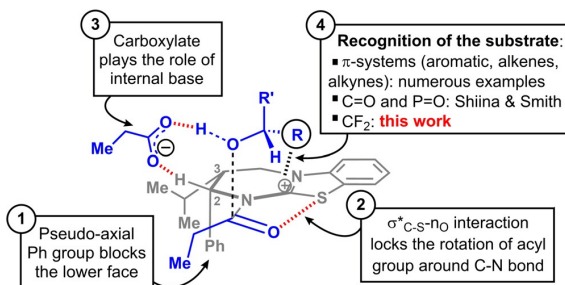


Figure 1. Relevant bioactive CF_2 -containing drugs.



Scheme 1. Accepted transition state for enantioselective acylation of secondary alcohols using HyperBTM.

- When an anhydride is used, the released carboxylate plays the role of an internal base, deprotonating the alcohol concomitantly to the C–O bond formation.
- For a good recognition, the alcohols should present a group that could interact with the cationic and/or aromatic part of the acylated catalyst.

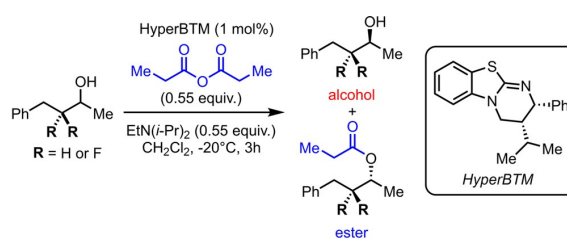
This last, but pivotal, interaction governs the intrinsic substrate selectivity and, as a result, the current scope of acylated alcohols has mainly been based on classical π -cation and/or a π - π interactions with aromatic, alkenyl or alkynyl groups.^[13] Interactions with C=O^[14] and P=O^[15] bonds were also described through the oxygen atom lone pair and the cationic part of the acylated isothioureia in the enantioselective acylation of secondary alcohols. More recently, Smith cleverly used a no-cation interaction to perform efficiently the kinetic resolution of tertiary alcohols.^[16]

In contrast with the well-studied and understood π interactions, the enantioselective acylation of α -fluorohydrins has been scarcely examined. Chen and co-workers explored the kinetic resolution of 2,2-difluoro-3-hydroxy-3-arylpropionates^[17a] and 2,2,2-trifluoro-1-aryl ethanol^[17b] using chiral benzotetramisole. The presence in these substrates of aryl substituents, known as strong directing groups, avoided the observation of any particular interaction due to the fluorinated moiety. More recently, in the context of the absolute configuration assignment of secondary alcohols, on an example of fluorohydrin, Rychnovsky observed a 2.5 faster rate of acylation of one enantiomer.^[18] On a trifluorohydrin, a 5.0 times rate acceleration was observed suggesting a possible interaction between the heteroatom and the cationic part of the acylated catalyst.

In the present study, we report the kinetic resolution (KR) of α,α -difluorohydrins by enantioselective acylation using a commercially available chiral isothioureia. The influence of the CF₂ group was compared with non-fluorinated analogues to evaluate its effect on the stereochemical outcome. In the absence of predominant cation- π interactions, this difluorinated group reveals to be a strong directing group ensuring the KR of various alcohols such as 4,4-difluoro-1,3-diols of interest with excellent levels of enantiocontrol. Turning to 2,2-difluoro-1,3-diols, we also demonstrated that aromatic and fluorinated groups were mutually compatible to provide the expected enantioenriched adducts with > 99:1 er. This report provides experimental and theoretical evidences for these different aspects enlarging the NCI involved in the acylation of alcohols/diols by chiral isothioureias.

Results and Discussion

To evaluate the impact of a CF₂ group on an alcohol KR selectivity, we first choose difficult substrates for the chiral isothioureias HyperBTM catalyzed acylation,^[19] namely 4-phenylbutan-2-ol **1a** and their fluorinated derivatives **1b-d** (Scheme 2). Unlike Chen's study,^[17a,b] the alcohols are not benzylic limiting the possibility of a classical enantiocontrol arising from π -interactions with the aryl group. As expected, alcohol **1a** exhibits a poor *s* value^[18] of 2 using standard



Racemic alcohols	1a	1b	1c	1d
yield ^a	42%	40%	42%	33%
(<i>er</i> _{alc}) ^b	(60.3:39.7)	(69.2:30.8)	(63.3:36.7)	(86.2:13.8)
yield ^a	41%	43%	44%	47%
(<i>er</i> _{est}) ^b	(62.7:37.3)	(70.3:29.7)	(64.9:35.1)	(80.9:19.1)
<i>C</i> ^c	45%	49%	47%	54%
<i>s</i> ^c	2	3.4	2.4	8.9

^a Isolated yields. ^b Determined by chiral HPLC, see SI for details. ^c *C* and *s* were calculated using Kagan's equations (Ref 19).

Scheme 2. KR of secondary alcohols using HyperBTM.

conditions with HyperBTM catalyst, further demonstrating the lack of stereodiscrimination between two aliphatic chains. Subsequently, fluorinated analogues **1b**, **1c** and **1d** were also acylated under the same conditions (See SI for the preparation of these three substrates). The *anti* and *syn* 3-fluoro-4-phenylbutan-2-ol **1b** and **1c** also provided moderate selectivities in accordance with Rychnovsky observation. In sharp contrast, presence of the difluoromethylene unit in alcohol **1d** considerably improved the substrate-catalyst recognition providing a *s* value of 8.9. Absolute configurations of each residual alcohols were determined using the mandelate method^[20] showing that **1a-d** major enantiomers possess a (*S*) configuration, which is in accordance with the Birman-Houk model of stereoselection.^[21] These results suggest that the CF₂ group plays the role of a directing group through electrostatic interaction.^[22] Interactions between positively charged nitrogen species and C-F bond had previously been identified on other scaffolds notably by the groups of O'Hagan and Gilmour.^[23] Comparison of the selectivity between **1a** and **1d** suggest that in the present acylation, the additional stabilization by the cation-F interaction is around 0.7 kcal mol⁻¹.

In order to get more insight on the interactions involved in the enantiodiscrimination, transition states (TS) for acylation of **1a,d** were computed on the enantiomeric HyperBTM through DFT methods completed by NBO analysis (see Supporting Information for details). According to the TS model described by Birman and Houk,^[10] the carboxylate acts as a relay base during the C–O bond formation (Figure 2). For non-fluorinated alcohols **1a**, computations provided a modest difference of 1.7 kcal mol⁻¹ between (*R*) and (*S*) enantiomer acylation TS. In sharp contrast, in the case of fluorinated **1d**, (*S*)-enantiomer TS was found to be 5.42 kcal mol⁻¹ lower in energy than the (*R*)-enantiomer TS. Most importantly, NBO revealed a stabilization between the catalyst and the substrate

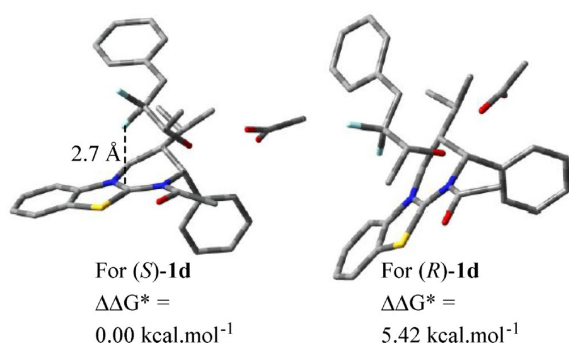
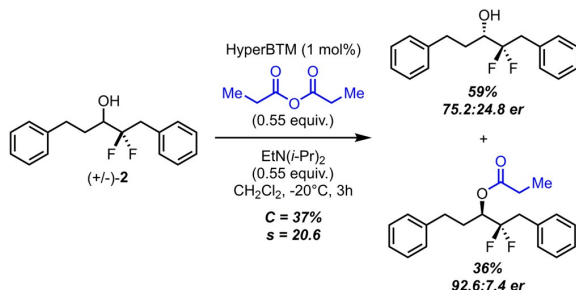


Figure 2. Computed transition states for **1d** acylation. Calculation were performed on (2*R*,3*S*)-HyperBTM catalyst.

observed through a C(NNS)-F interaction. For both enantiomers, the C(NNS)-F are interacting at a distance of 2.7 Å, strongly rigidifying the system. As a result, for the (*S*)-enantiomer, the methyl substituent points on the top face while for the (*R*)-enantiomer, the location of this methyl on the bottom face near to the catalyst generates a strong destabilization which needs a shorter O-C(O) distance to attain the TS. Interestingly, if the NBO analysis revealed F-C(NN) NCI for both enantiomers, the NBO energy of (*S*)-enantiomer is largely higher compared to the (*R*) one. Consequently, and as observed for the TS studies of the acylation of alcohols **1a-d**, the TSs occur at an early stage of the reaction as revealed by the O...CO distance measurements for the preferred *S* enantiomers.

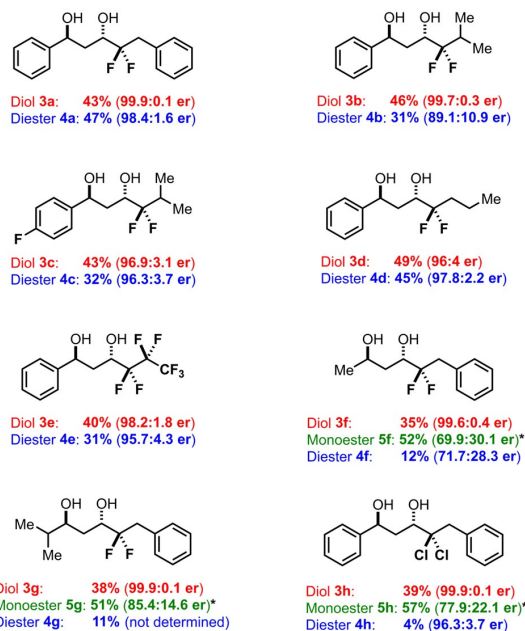
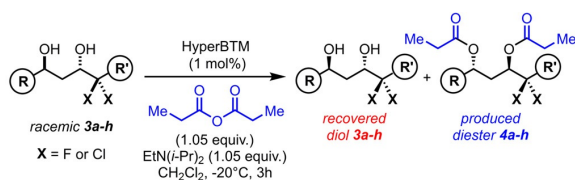
In order to further establish this CF₂ recognition ability, a challenging pseudo-symmetric aliphatic alcohol **2**, differentiated only by the presence of two fluorine atoms on one arm was studied under the standard KR conditions (Scheme 3). Confirming our initial finding, a *s* value of 20.6 was obtained generating the enantioenriched ester in 36% yield and 92.6:7.4 er. This important result highlights the potential of the CF₂ substituent as a strong recognition anchor for organocatalyzed acylation of fluorohydrins.

Having established the CF₂ group recognition ability, we further exemplified this principle through the acylation of more complex and valuable *anti*-1,3-diols. It is noteworthy that such kind of scaffolds, CF₂ analogues of naturally occurring 1,3-diols were not explored in the enantioselective

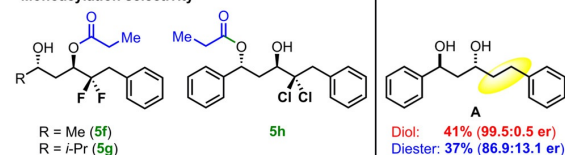


Scheme 3. KR of 2,2-difluoro alcohol **2**.

series. Given the recent interest at modifying natural 1,3-diols properties through fluorine insertion,^[24] developing an enantioselective access to a new type of bis-fluorinated 1,3-diols would be highly attractive. The racemic substrates were easily prepared in a two-step sequence involving an organocatalyzed one-pot difluorination/copper-catalyzed aldol reaction of aldehydes^[25] followed by an *anti* reduction of the corresponding difluorinated α -hydroxyketones^[26] (see SI for details). Different substrates, with an *anti* 4,4-difluoro-1,3-diol framework, were then submitted to the conditions of enantioselective acylation with HyperBTM as catalyst (Scheme 4). For diols possessing one benzylic alcohol **3a-e**, high levels of enantioselectivity were obtained for both recovered diols and produced diesters, with up to 99.9:0.1 er and 98.4:1.6 er, respectively. The excellent yields and er observed for the diesters confirm that with such bifunctional substrates, an



* Monoacylation selectivity



Scheme 4. DoCKR of *anti* 4,4-difluoro-1,3-diols.

additive Horeau-type amplification takes place through a double catalytic kinetic resolution (DoCKR).^[13f] This indicates that on one alcohol, enantiodiscrimination occurs through interaction with the aromatic substituent while on the other alcohol, the CF₂ group acts as the recognition moiety.

In order to check the importance of the CF₂ group over the DoCKR in these diols, we compared the KR of diol **3a** with the one of diol **A**, possessing the parent non-fluorinated aliphatic chain (Scheme 4).^[13f] While diester **4a** was isolated in 98.4:1.6 er, diester derived from **A** was obtained in a much lower 86.9:13.1 er. This confirms that two highly selective events are occurring through the double acylation in the case of fluorinated diols **3a–e**. As a result, different fluorinated diols possessing various side chains, such as benzyl (**3a**), isopropyl (**3b** and **3c**), propyl (**3d**) and even a perfluorinated group (**3e**), were kinetically resolved with success.^[27]

We then scrutinized the KR of more challenging aliphatic diols **3fg** lacking the first benzylic directing group. Gratifyingly, the presence of the difluoromethylene unit enabled a successful catalyst recognition providing the recovered diols with almost perfect enantioselectivity (99.6:0.4 to 99.9:0.1 er) and 35–38% yield. These two results suggest an *s* factor for the acylation of fluorinated aliphatic alcohols above 15 through the single cation–F stabilization.^[28] Confirming the role of the CF₂ group, highly enantioselective acylation occurs at the most acidic difluorohydrins while acylation of the second aliphatic alcohols is much slower leaving a large amount of unreacted monoester. It is noteworthy that diesters, generated in small amount, have the same enantiomeric ratio than the monoesters, further highlighting the lack of stereocontrol during the second acylation of simple aliphatic alcohols.

In order to check the influence of the nature of the halogen atoms, racemic dichlorinated diol **3h**, an analogue of difluorinated **3a** was prepared. During the KR of **3h**, a large amount of monoester **5h** was formed with preferential acylation on the benzylic hydroxyl group. However, diester **4h**, formed in small amount, has a greater enantioselectivity (96.3:3.7 er) than the monoester (77.9:22.1 er). Altogether, these results suggest that the increased steric hindrance around the dichlorohydrin decreases the reactivity while the CCl₂ unit can also be considered as a recognition anchor for a selective recognition.

All the above results demonstrate that the CF₂ unit can act as a powerful directing group in the isothioureia catalyzed enantioselective acylation. Given the observed catalytic recognition, we next questioned about the selectivity of the KR of alcohols possessing two competing units. For this purpose, we decided to study the DoCKR of *anti* 2,2-difluoro-1,3-diols bearing classical π -systems on both sides.

As already mentioned, given the importance of the *anti* 1,3-diol motifs, developing fluorinated analogues is of great interest. However, only two studies reported the enantioselective synthesis of *anti* 2,2-difluoro-1,3-diols, respectively by the group of Clarke^[29] and the group of Wolf.^[30] The first team performed a double reduction of a single 1,3-diketone using a chiral ruthenium complex allowing the formation of the corresponding chiral diol contaminated with poor diastereoselectivity (*anti:meso* 68:32 and 86:14 er). Wolf and

co-workers developed a catalytic aldol reaction using difluorinated ketone analogues albeit with moderate enantiocontrol (typically around 90:10 er). They demonstrated on a single case a successive *anti*-selective reduction leading to 2,2-difluoro-1,3-diols with 94:6 er. As a result, discovering a general approach to obtain such kind of diols in high level of enantioselectivity is highly desirable. For the DoCKR process, the racemic *anti* 2,2-difluoro-1,3-diols were easily prepared through a single step by an aldolization-Tishchenko reaction starting from an α,α -difluoroketone and an excess of aldehyde under basic conditions.^[31] Racemic C₂-symmetrical and unsymmetrical substrates were easily prepared through this procedure and tested in an acylative KR.

Given the recognition ability of the CF₂ unit, competition by recognition through aromatic and CF₂ groups located on the sides of the two alcohols would considerably decrease the enantiocontrol. However, starting from diol **6a**, excellent selectivity was observed and both diol and diester were isolated almost enantiopure with yields close to 50%, indicating that the cation– π interactions is by far stronger than the cation–F one (Scheme 5). These results are in the same range than for non-fluorinated analogue **B**,^[13f] confirming this predominance of the recognition by the aromatic substituent.

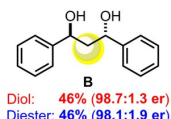
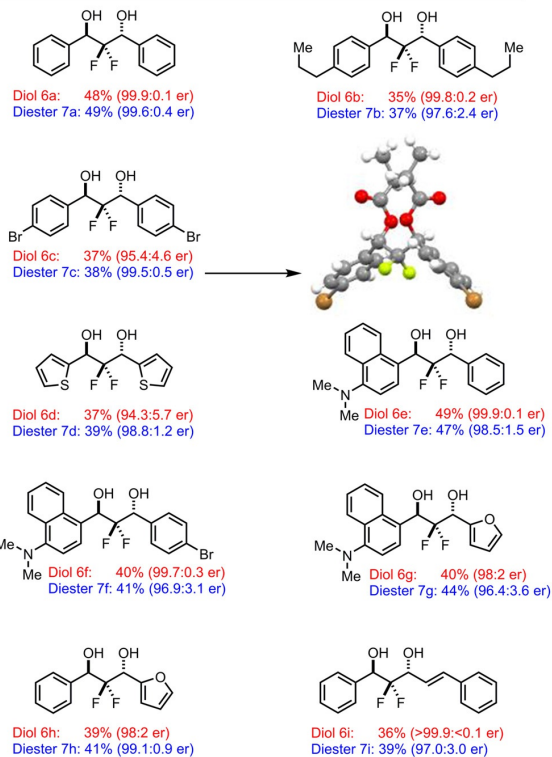
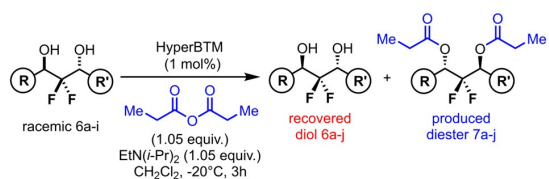
This excellent enantiocontrol was found to be quite general using other *anti* 2,2-difluoro-1,3-diols with different substituents on the aromatic rings (**6b**, **6c**) or with hetero-aromatic group (**6d**) (Scheme 5). In all cases, both diols and diesters were obtained with excellent enantioselectivity while only minor amount of mono-ester is formed. Unsymmetrical diols were also successfully employed in the DoCKR process (**6e–j**). Styrenyl substituent (**6i**) was also tested affording also excellent results in terms of yields and enantioselectivities. Single crystal X-ray diffraction of diester **7c** confirmed the absolute configuration in these series.^[32]

The beneficial effect of two successive KR events was pointed out with the single KR of monoester **8** (Scheme 6). An impressive *s* value of 75 is observed, confirming that the excellent er observed for the diesters in Scheme 5 are due to a second stereocontrol by the catalyst during the acylation, through DoCKR.

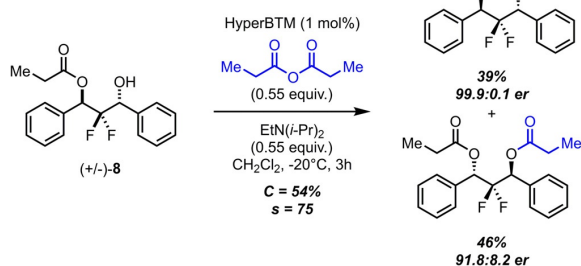
In order to highlight the versatility of these chiral building blocks, diol **6a** was converted to bis-tosylamide **9** (Scheme 7). The transformation involves a four-steps sequence featuring the activation of hydroxyl groups as mesylates, displacement by sodium azide through a S_N2 mechanism, reduction of the bis-azide to a diamine before tosylation affording compound **9**, potentially valuable diamine ligand.

Conclusion

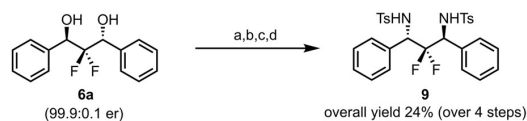
In this study, we carefully studied the impact of α,α -difluorohydrins on the organocatalyzed acylative kinetic resolution. We discovered that, in the absence of recognition based on interaction with an aromatic moiety, this new class of reagent undergoes KR with excellent selectivity through interaction between one fluorine and the cationic organocatalyst. This non-covalent interaction (NCI) with fluorine,



Scheme 5. DoCkR of *anti* 2,2-difluoro-1,3-diols.



Scheme 6. KR of 2,2-difluoro alcohol **8**.



a- MsCl, Et₃N, DMAP (cat.), CH₂Cl₂, 0°C, **84%**; b- NaN₃, DMF, 100°C, **79%**; c- H₂, Pd/C, MeOH, rt, **68%**; d- TsCl, Et₃N, DMAP (cat.), CH₂Cl₂, rt, **53%**.

Scheme 7. Post-transformation of diol **6a**.

involved for the first time in the organocatalyzed acylation of alcohols, was proven from experimental and theoretical points of view. The deeper understanding of the network of NCI led us to develop a synthetic method to prepare a large variety of highly enantioenriched organofluorine compounds. As a result, in a broad array of α,α -difluorohydrins such as *anti* 4,4-difluoro-1,3-diols (**3a–h**), both alcohols and esters can be isolated with exquisite levels of enantiocontrol (typically above 98:2 er). When starting from *anti* 2,2-difluoro-1,3-diols, excellent enantioselectivity are observed highlighting that both recognition by the aromatic group and C(sp³)F₂ effect are not competing. Through this study, 18 examples of α,α -difluorohydrins of potential strong synthetic interest were generated in good to excellent enantioselectivity. Overall, this study increases the recognition toolbox with a new type of functional group and unlocks the enantioselective preparation of a broad array of valuable fluorinated diols.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: acylation · alcohols · difluoromethylene group · isothiourea · organocatalysis

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