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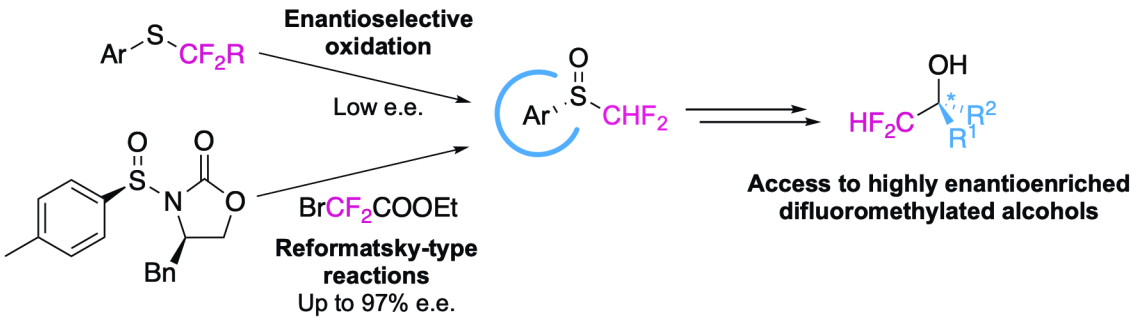

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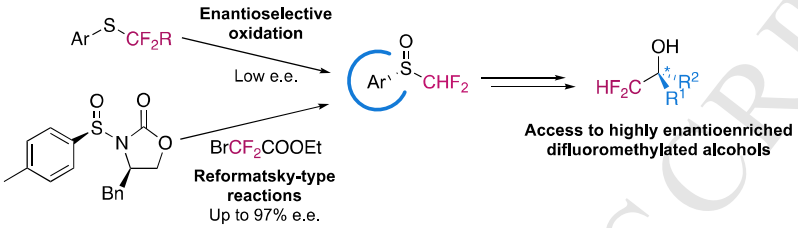

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Efficient asymmetric synthesis of aryl difluoromethyl sulfoxides and their use to access enantiopure α-difluoromethyl alcohols

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ABSTRACT

The -CHF_2 moiety has shown a growing interest in pharmaceutical and agrochemical applications over the last few years. Its introduction is therefore a current research topic for organic chemists. Several groups have reported the synthesis of difluoromethylated compounds. However, the more challenging enantioselective introduction of the difluoromethyl group has been scarcely described yet. We recently developed a new strategy, based on the use of an enantiopure difluoromethyl sulfoxide used as chiral and traceless auxiliary, for the synthesis of highly enantioenriched α-difluoromethyl alcohols.[8] The first method developed in our laboratory aims to access highly stereoenriched α,α-difluoro-β-hydroxysulfoxides through the condensation of the enantiopure difluoromethyl sulfoxide on carbonyl derivatives. It is noteworthy that highly diastereo- and enantioenriched α,α-difluoro-β-hydroxysulfoxides can also be accessed after the diastereoselective reduction of highly enantioenriched α,α-difluoro-β-ketosulfoxides. Finally, the expected difluoromethyl-substituted alcohols can be obtained after removal of the chiral auxiliary with complete retention of stereoenrichment at carbon.

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1. Introduction

Nowadays, fluorine plays an increasingly important role in various areas of our daily lives. The improved physical, chemical and biological properties of drugs or agrochemicals bearing fluorinated moieties have indeed been widely studied and highlighted over the past few years.[1] Consequently, the development of new methodologies for the introduction of fluorinated substituents – F, CF_3, OCF_3, SCF_3, $C_mF_nH_p$, etc. – has become an important subject of research for organic chemists. Moreover, their stereoselective introduction is even more challenging.

Recently, several groups focused their efforts on the introduction of the CHF_2 moiety. This fluorinated group, in addition to impacting the acidity, metabolic stability, lipophilicity or even conformational preference of biologically active compounds, is also known to be a good hydrogen bond donor and a bioisostere of hydroxy, thiol and amide groups.[2] These outstanding properties led chemists to develop several methods for its non-stereoselective introduction.[3] In contrast, a limited ~~number of~~ examples describe the enantioselective synthesis of molecules bearing this CHF_2 moiety.[4] This is for instance the case for the synthesis of highly enantioenriched α-difluoromethyl alcohols. They can be accessed through bio- and organometallic reductions of α,α-difluoro ketones,[5] pallado-catalyzed reductive coupling[6] or enantioselective difluoromethylations involving naked CHF_2^- anion surrogates in presence of different chiral quaternary ammonium salts for instance.[4a, 7] Recently, we also reported a new enantioselective method to access these building blocks.[8]

2. Results and discussion

2.1. Description of the strategy

As outlined above and in contrast to enantioselective fluorination or even trifluoromethylation, the enantioselective introduction of a difluoromethyl group is in its infancy. In our willingness to contribute to the development of new methodologies to access highly enantioenriched α-difluoromethyl alcohols, it was chosen to use enantiopure aryl difluoromethyl sulfoxides, their non-fluorinated analogues being known as excellent chiral inductors employed in the synthesis of a huge

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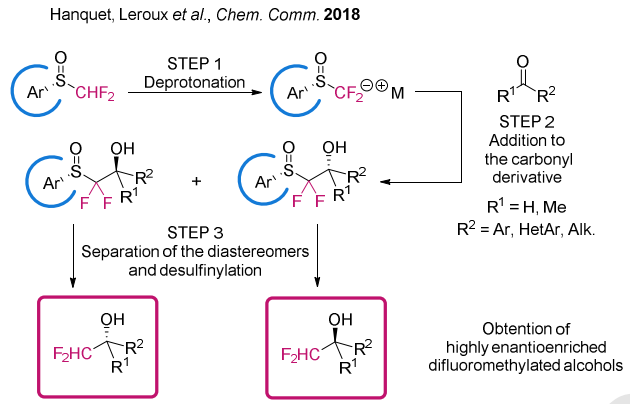
number of optically pure compounds.[9] This kind of difluoromethyl group attached to an electron-withdrawing substituent can be readily deprotonated and trapped with a variety of electrophiles, such as aldehydes and ketones. After separation of the diastereomers of the α,α-difluoro-β-hydroxysulfoxides and removal of the chiral auxiliary, this strategy allows to access highly enantioenriched α-difluoromethyl alcohols (Scheme 1).[8]

The presence of a sulfanyl, sulfinyl or sulfonyl group in α position of a carbanion is known to stabilize this anionic species. This effect has therefore been widely explored and discussed over the last decades. It has been rationalized by different hypotheses, such as the possibility of back-donation of the lone pair of electrons of the carbanion into the vacant d-orbitals of the sulfur derivative,[10] polarizability of sulfur[11] or more recently, negative hyperconjugation.[11b, 11d, 12]

Moreover, in the case of fluorinated carbanions, their substitution with softening groups in α position, such as arylsulfonyl or arylsulfinyl groups, is also a useful approach to alleviate the negative fluorine effect and enhance the nucleophilicity of the RCF_2^- species.[13]



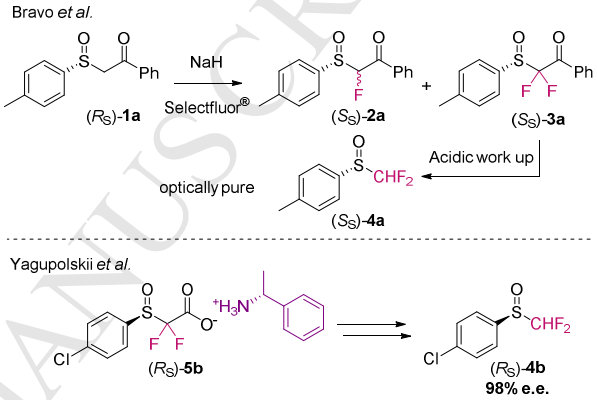
Scheme 1. Access to highly enantioenriched α-difluoromethyl alcohols – Using sulfoxides as chiral and traceless auxiliaries

This kind of strategy involving a difluoromethylated arylsulfonyl group has been extensively studied by Olah, Prakash and Hu, amongst others.[14] However, the chemistry using an arylsulfinyl group has been rarely explored yet. For instance, the same scientists successfully achieved non-stereoselective nucleophilic (phenylsulfinyl) difluoromethylation of both enolizable and non-enolizable aldehydes and ketones by using racemic difluoromethyl phenyl sulfoxide as fluoroalkylating agent.[15] Unfortunately, even if they managed to synthesize α,α-difluoro β-hydroxysulfoxides with good yields, the diastereomeric excesses associated were low (diastereomeric ratios ranging between 49:51 and 33:67). This work was considered as the starting point of our project.

In our case, the use of an enantiopure difluoromethyl sulfoxide was required to access highly enantioenriched α,α-difluoro-β-hydroxysulfoxides and α-difluoromethyl alcohols (Scheme 1).[8] This strategy will be discussed in detail in this paper. We will first present the numerous trials that were carried out in the aim of synthesizing an enantiopure aryl difluoromethyl sulfoxide. Then, several experiments run in order to evaluate and improve the diastereoselectivity of the addition of the sulfoxide anion to carbonyl derivatives will be discussed. A new way to access diastereopure α,α-difluoro-β-hydroxysulfoxides, inspired by the well-known diastereoselective reduction of non-fluorinated β-ketosulfoxides, will be highlighted.[16] And finally, the different strategies that have been employed to remove the chiral auxiliary will be presented.[17]

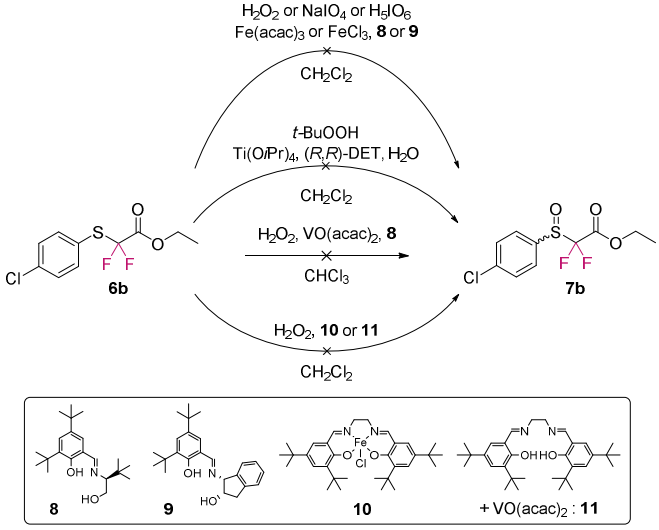
2.2 The quest for an enantiopure aryl difluoromethyl sulfoxide

This investigation started focusing on the synthesis of a highly enantiopure aryl difluoromethyl sulfoxide. To the best of our knowledge, only two groups managed to obtain this kind of sulfoxide. Such compound had first been serendipitously obtained as a degradation product by Bravo and co-workers in their attempts to synthesize enantiopure α-monofluoro-β-ketosulfoxides (Scheme 2).[18] Shortly after this work, the access to an enantiopure aryl difluoromethyl sulfoxide was studied by the group of Yagupolskii.[19] They managed to synthesize highly enantioenriched optically active *p*-chlorophenyl difluoromethyl sulfoxide (R_S)-**4b** with 98% e.e. Unfortunately, the strategy consisted in a multi-step process involving a chiral resolution of an arylsulfinyldifluoroacetic acid and the use of difficult-to-handle intermediates. It was therefore decided to search for another efficient method to generate highly enantioenriched aryl difluoromethyl sulfoxides.



Scheme 2. Two existing strategies to access highly enantioenriched α-difluoromethyl alcohols

Different enantioselective sulfoxidations of prochiral sulfides usually employed to access enantiopure non-fluorinated sulfoxides were first tested (Scheme 3). Oxidation of ethyl *p*-chlorophenylthiodifluoroacetate **6b**, by using either the modified Sharpless reagent[20] or different oxidizing systems composed of iron or vanadium complexes with Schiff bases **8** and **9**[21] or, as a start, achiral salens **10** and **11**,[22] as ligands, were unfortunately unsuccessful, even after several days of reaction. The simultaneous presence of the ester group and of two fluorine atoms might be responsible for the low reactivity of the sulfide, rendering it more electron deficient and less prone to be oxidized.



Scheme 3. Attempts of enantioselective sulfoxidations

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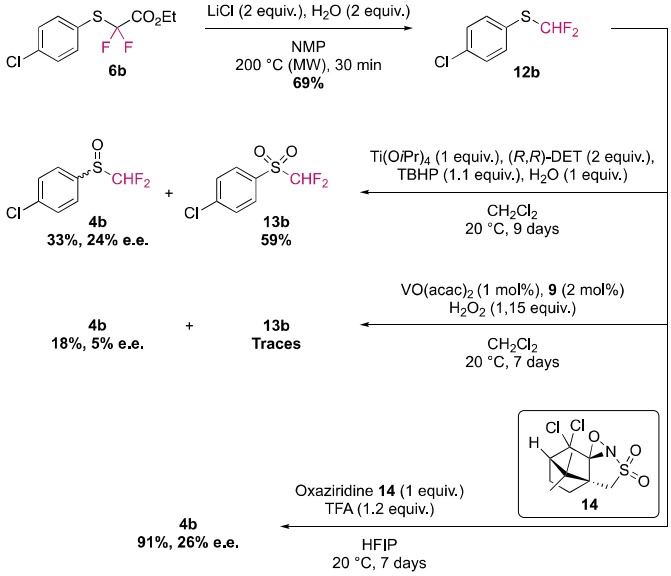
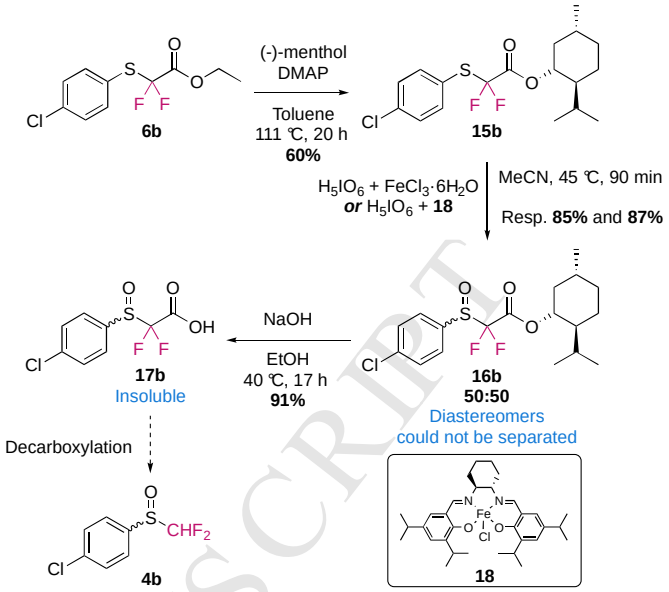
It was therefore decided to test those conditions on the corresponding difluoromethyl sulfide **12b** obtained through decarboxylation of compound **6b** (Scheme 4). This species is less electron-deficient and sterically less hindered than compound **6b** due to the absence of the ester group and should consequently be more reactive towards oxidation.



Scheme 4. Preparation of a less electron-deficient sulfide and attempts for its enantioselective sulfoxidation

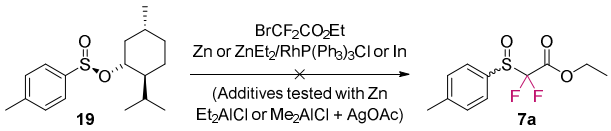
The expected sulfoxide could indeed be obtained through oxidation using Kagan's conditions involving the modified Sharpless reagent (*Scheme 4*).[20] However, after a rapid optimization, only 24% of enantiomeric excess was obtained at best for compound **4b**. Moreover, large amounts of the corresponding sulfone **13b** were obtained due to overoxidation of sulfoxide **4b** and nine days of reaction were required (See supplementary data for optimization table). The use of the oxidizing system composed of Schiff base **9**, $VO(acac)_2$ and H_2O_2 on sulfide **12b** also led to a small conversion into the expected sulfoxide after one week of reaction at room temperature (*Scheme 4*).[21a] Unfortunately, difluoromethyl sulfoxide **4b** was obtained with only 5% e.e. *Finally,* Davis' camphorsulfonyl oxaziridine **14** was tested as a stoichiometric chiral oxygen-transfer agent on sulfide **12b** (Scheme 4).[23] After a rapid optimization (See supplementary data for details), running the reaction in HFIP as solvent gave positive results, affording **4b** with 91% conversion and 24% e.e. after seven days of reaction. Due to the long reaction times required and to the low enantiomeric excesses and conversions obtained in most cases, such methods were set aside for the benefit of other strategies.

A diastereoselective pathway was then attempted to access the desired enantiopure aryl difluoromethyl sulfoxide **4b** (Scheme 5). For this purpose, it was decided to introduce (-)-menthol as a chiral auxiliary. The synthesis of enantiopure menthyl (4-chlorophenyl)thio)-2,2-difluoroacetate **15b** was performed through transesterification of sulfinyl acetate **6b**. We believed that the oxidation of this prochiral sulfide with periodic acid and $FeCl_3{\cdot}H_2O$ could be selective due to the presence of the chiral menthyl group and/or afford a mixture of separable diastereomers. It was also envisaged to use iron salen complex **18** in presence of periodic acid as a chiral oxidizing agent. However, not only the sulfoxidation was not diastereoselective in both attempts, certainly due to the distance between the sulfide and the chiral auxiliary in the first case, but it was also impossible to separate the diastereomers of **16b** by usual purification methods. Otherwise, it could have been possible to get the expected sulfoxide **4b** after saponification of diastereopure **16b** followed by a decarboxylation step, or even by a direct Krapcho dealkoxycarbonylation-type reaction[24] on **16b**.



Scheme 5. Attempts to access highly enantioenriched sulfoxide **4b** by using L-menthol as a chiral auxiliary

After these unfruitful trials, it was decided to perform Reformatsky-type reactions using ethyl bromodifluoroacetate and enantiopure (-)-menthyl (*S*)-*p*-toluenesulfinate **19** in presence of zinc, previously activated with HCl (Scheme 6).[25] No conversion was obtained even by activating menthyl sulfinate **19** with diethyl- or dimethylaluminium chloride in presence of silver acetate. Honda's method[26] involving a solution of diethylzinc in presence of Wilkinson's catalyst was also tried but unfortunately, the starting material was again totally recovered. Finally, indium beads were tested but no conversion was obtained.[27]



Scheme 6. Attempts to synthesize enantiopure sulfoxide **7a** by performing Reformatsky-type reactions on enantiopure (-)-menthyl (*S*)-*p*-toluenesulfinate **19**

As chiral sulfinyloxazolidinones have been described as hundred times more reactive than menthyl sulfinate **19**,[28] compound (R_S,*R*)-**20** was tested as starting material for those Reformatsky-type reactions (Table 1). To our delight, and as previously shown by our group,[8] the reaction using zinc activated with HCl gave access to ethyl α,α-difluoro-(*p*-tolylsulfinyl)-acetate (S_S)-**7a** with a good yield and an enantiomeric excess of up to 97% (Entry 1). The Honda-Reformatsky reaction using diethylzinc and Wilkinson's catalyst also allowed us to obtain (S_S)-**7a** with slightly lower yield and enantiomeric excess (resp. 65% and 86% e.e., Entry 2). Unfortunately, reaction with indium only gave low conversion (< 9%, Entry 3). This reaction was optimized and highly enantioenriched sulfinyl acetate (S_S)-**7a** was obtained with good yield by using diethylzinc without catalyst (79% yield and 90% e.e., Entry 4). In this way, the pre-activation of zinc powder is not necessary. Finally, and as previously described,[8] highly enantioenriched difluoromethyl *p*-tolyl sulfoxide (S_S)-**4a** was obtained after decarboxylation of enantioenriched sulfinylester (S_S)-**7a**, followed by recrystallisation from diethyl ether.

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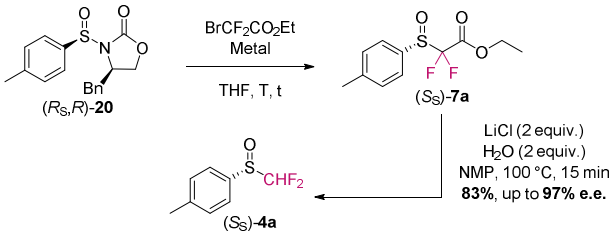
Table 1. Synthesis of highly enantioenriched sulfoxide (S_S)-**4a** by performing Reformatsky-type reactions on enantiopure sulfinyloxazolidinone[8] (R_S,*R*)-**20**

Hanquet, Leroux *et al.*, *Chem. Comm.* **2018**



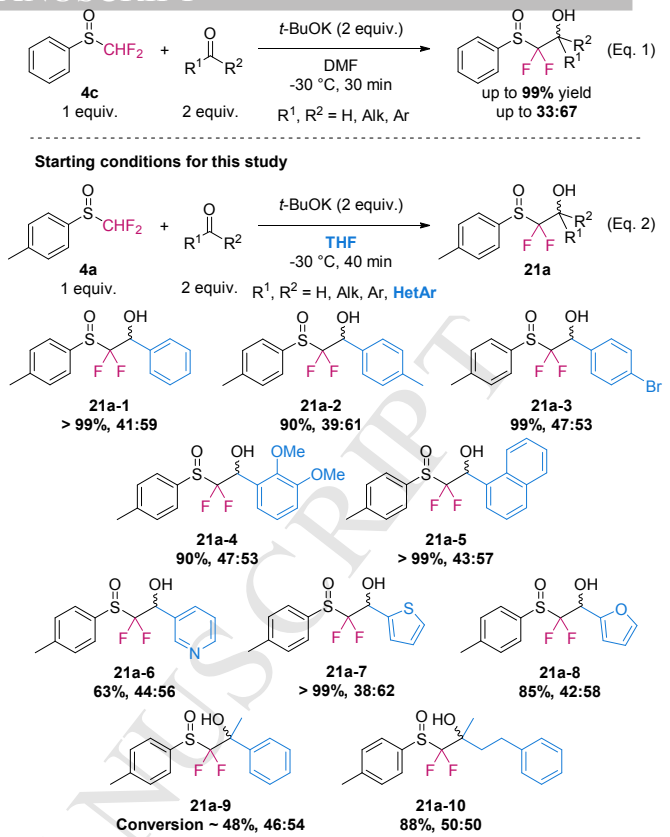
Entry	$BrCF_2CO_2Et$ (equiv.)	Metal (equiv.)	T (°C)	t (h)	Yield of 7a (%)	e.e. of 7a (%)
1	2.4	Zn (2.4)	66	41	**72**	**97**
2	3.0	$ZnEt_2$[a] (2.0)	-20	1	**65**	**86**
			20	4		
3[b]	2.0	In (2.0)	66	48	< **9**[c]	-
4	3.0	$ZnEt_2$ (2.0)	20	4	**79**	**90**

[a] 3 mol% of Wilkinson's catalyst were added to the reaction mixture – [b] The reaction was tested on the achiral non-substituted sulfinyloxazolidinone – Conversions were determined by ^{19}F NMR spectroscopy.

2.2. Evaluation of the diastereoselectivity of the synthesis of α,α-difluoro-β-hydroxysulfoxides under different conditions

Once an efficient pathway to access to enantiopure difluoromethyl sulfoxide (S_S)-**4a** was found, further efforts were focused on its deprotonation, followed by its addition to different carbonyl derivatives. In contrast to the group of Hu and Prakash (Eq. 1, *Scheme 7*),[15] it was decided to use THF, a safer and eco-friendlier solvent than DMF. *First, a* quick screening of several alkyl, aryl and even heteroaryl aldehydes and ketones *was successfully* performed. Yields were mostly high, but as expected *from the work of Hu and Prakash*, the diastereoselectivities were still low (yields up to > 99%, d.r. up to 38:62, Eq. 2, *Scheme* 7). A study to improve this diastereoselectivity *had therefore to be* carried out. *This was a challenge, since precedents in literature on non-fluorinated analogues showed that* the diastereoselectivity of the addition of non-fluorinated sulfoxides on carbonyl derivatives is generally very poor, whatever the conditions used, the nature of the sulfoxide substituents or the chelating metal employed.[29b,30]

Nevertheless, starting from our previous results, the investigation began with the addition of different reagents, among which chelating or complexing agents for instance, into the reaction mixture (Eq. 2, Scheme 7, Table 2). Unfortunately, using $BF_3.OEt_2$ or $Sc(OTf)_3$ did not give any conversion (Entries 2 and 3). It was possible to get the desired α,α-difluoro-β-hydroxysulfoxides with $TiCl_4$ or $ZnCl_2$ (Entries 4 and 5). However, the diastereoselectivities obtained were as low as those observed without chelating agent (Entry 1). A crown ether (2,3,11,12-tetracarboxylate-substituted 18-crown-6, Entry 6) able to complex the potassium cation coming from the inorganic base,[31] was also tested. This complexation would generate an almost 'naked anion', more nucleophilic than the non-complexed species.[32] This increased reactivity might have had an impact on the reaction rate as well as on the organization of the transition state, and therefore on the diastereoselectivity. Unfortunately, when using this macrocycle, the conversion was low and the diastereomeric ratio was unchanged.



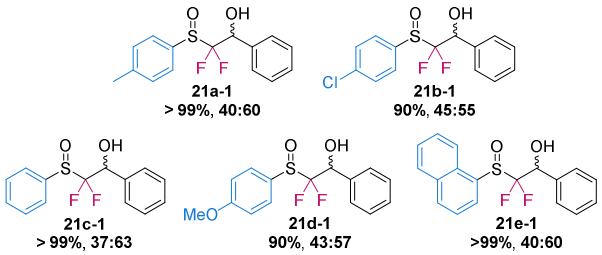
Scheme 7. First screening of different carbonyl derivatives

Table 2. Attempts to improve the diastereomeric ratio of **21a-5** by using different reagents (carbonyl derivative = 1-naphthaldehyde)

Entry	Additive	Conversion of 4a (%)[a]	d.r. 21a-5
1	-	**100**	**43:57**
2	$BF_3{\cdot}OEt_2$	**0**	-
3	$Sc(OTf)_3$	**0**	-
4	$TiCl_4$	**47**	**44:56**
5	$ZnCl_2$	**100**	**43:57**
6	(+)-2,3,11,12-$(CO_2H)_4$-18-C-6[b]	**35**	**44:56**

[a] Conversions and d.r. were determined by ^{19}F NMR spectroscopy – [b] See experimental part for details.

Different aryl sulfoxide derivatives were then tested to see if some improved diastereoselectivities could be observed (Scheme 8). Five different sulfoxides were synthesized according to the procedure that was developed in our group (see experimental section for their synthesis).[8] Slightly better diastereomeric ratios were observed when the phenyl **21c-1**, *p*-tolyl **21a-1** and 1-naphthyl **21e-1** derivatives were used (resp. 37:63, 40:60 and 40:60) in comparison to the *p*-chloro **21b-1** and *p*-methoxy **21d-1** derivatives (resp. 45:55 and 43:57).



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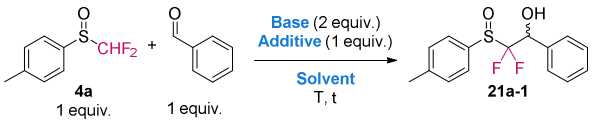
Scheme 8. Attempts to improve the diastereoselectivity by changing the aromatic ring of the sulfoxide (Base:sulfoxide:electrophile = 2:1:2)

This investigation continued with the screening of different bases in order to evaluate their impact on the diastereoselectivity of the synthesis of α,α-difluoro-β-hydroxysulfoxides (Table 3).

Table 3. Results obtained for the screening of different bases



Entry	Base (2 equiv.)	Solvent	T (°C)	T (h)	Conversion[a] (%)	d.r. 21a-1[b]
1	*t*-BuOK	DMF	-30	2	**100**	**54:46**
2		THF	-30	0.5	**100**	**41:59**
3	KHMDS	DMF	-30	1	**100**	**53:47**
4		THF	-30	1	**96**	**40:60**
5	KHMDS	DMF	-30 20	24 72	*90* (**45**)	-
6	+ 18-C-6	THF	-30 20	24 72	*100* (**traces**)	-
7	LiHMDS	DMF	-30 20	3 12	*45* (**37**)	**45:55**
8		THF	-30	3	*98* (**92**)	**38:62**
9	LiHMDS	DMF	-30 20	24 72	*33* (**18**)	**60:40**
10	+ 12-C-4	THF	-30 20	24 72	*80* (**69**)	**36:64**
11	NaH	THF	-78 20	2 1	**100**	**59:41**
12	P_4t-Bu[c]	DMF	-30	2	*100*	**98:2**
13		THF	-30	2	*100*	**84:16**

[a] Conversions were determined by ^{19}F NMR spectroscopy; in *italics*, the percentage of sulfoxide **4a** converted, in **bold**, the conversion into **21a-1** – [b] Diastereomeric ratios were determined by ^{19}F NMR spectroscopy – [c] P_4t-Bu stands for $[(Me_2N)_3P{=}N]_3P{=}N$-*t*Bu and was used as a commercially available solution in hexane.

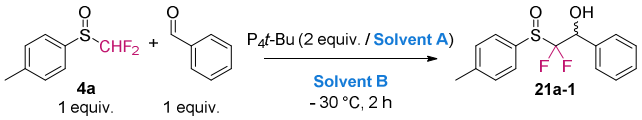
By using potassium *tert*-butoxide the conversion into the desired α,α-difluoro-β-hydroxysulfoxide was high in either DMF or THF after 40 minutes of reaction at –30 °C (Entries 1 and 2). Unfortunately, the observed diastereoselectivities were low (41:59 in THF and 54:46 in DMF). The same kind of results were observed with KHMDS after one hour at –30 °C (53:47 in DMF *vs.* 40:60 in THF, Entries 3 and 4). KHMDS was also tested in presence of 18-crown-6 (18-C-6), to generate a more nucleophilic carbanion such as in Table 2 , but unfortunately after several days of reaction a lot of side-products were obtained (Entries 5 and 6). Reactions using LiHMDS as a base were then carried out and monitored by TLC. Almost full conversion was obtained in THF (Entry 8), but the reaction reached only 45% conversion in DMF (Entry 7). Concerning the diastereomeric ratios, they were similar to the ones that were usually obtained (45:55 in DMF *vs.* 38:62 in THF). By using 12-crown-4 (12-C-4) to complex the lithium cation, conversions were less interesting and the diastereomeric excesses still low (Entries 9 and 10). A trial carried out in THF with 2 equivalents of sodium hydride showed full conversion but poor diastereoselectivity (Entry 11). Finally, and as described in our recent paper,[8] Schwesinger's superbase, P_4t-Bu was tested and gave good results (Entries 12 and 13). In both cases, total conversions of **4a** were observed and diastereomeric excesses up to 96% were reached in DMF (Entry 12).

This base had been involved in the deprotonation of fluoroform[33] and difluoro(phenylsulfanyl)methane[34] to generate stabilized 'naked' carbanions with increased reactivity towards electrophiles. In our case, and in contrast to other cations such as Li^+, K^+ or Mg^{2+}, having the non-coordinating counterion $[P_4t\text{-}Bu/H]^+$ was thought to increase the nucleophilicity of the anion of difluoromethyl *p*-tolyl sulfoxide **4a**, thus generating an earlier transition state for the attack on the carbonyl derivatives. The attack of the sulfoxide carbanion being fastened, the carbonyl derivatives would keep a close-to-planar C-sp^2 geometry in the transition state, rather than a generally more favored C-sp^3-like tetrahedral geometry. In this way, by using P_4t-Bu, a more efficient relay of the chirality from the sulfoxide to the α,α-difluoro-β-hydroxysulfoxide was first expected.

As explained in our previous work,[8] some problems of reproducibility were encountered for the reaction performed in DMF (d.r. varying between 55:45 and 99:1, Entry 1, Table 4). This would mainly be due to the formation of aggregates in the reaction mixture, probably coming from the non-miscibility of hexane –solvent in which P_4t-Bu is commercially available– and DMF, or by the fact that the superbase is not soluble in DMF.[35]

A screening of different solvents was performed (Table 4). Practically, hexane from the commercially available solution was removed under vacuum from the desired amount of P_4t-Bu. The superbase was then solubilized in the desired solvent, solvent A, at –30 °C. This solution was then added dropwise onto the mixture composed of sulfoxide **4a** and benzaldehyde, previously dissolved in solvent B at –30 °C. In each case, the conversions of **4a** were excellent (Entries 2 to 7). The highest ratios were nevertheless observed when THF was involved as solvent A (Entry 5), solvent B (Entry 2) or both of them (Entry 7). The best reproducible diastereomeric ratio being obtained when only THF was used (Entry 7), this combination was therefore chosen for the following experiments of this study.

Table 4. Screening of different solvents to evaluate their impact on the diastereoselectivity and reproducibility of the reaction



Entry	Solvent A	Solvent B	Conversion of 4a[a] (%)	d.r. 21a-1[b]
1[c]	Hexane[d]	DMF	**100**[e]	**55:45 to 99:1**
2[c]	Hexane[d]	THF	**100**	**84:16**
3	DMF[f]	DMF[g]	**100**	**61:39**
4	Et_2O[f]	DMF	**100**	**56:44**
5	THF[f]	DMF	**>99**[e]	**93:7**
6	Et_2O[f]	Et_2O	**>99**	**60:40**
7	THF[f]	THF	**>99**[d]	**> 98:2**

[a] Conversions were determined by ^{19}F NMR spectroscopy – [b] Diastereomeric ratios were determined by ^{19}F NMR spectroscopy – [c] Results taken from ref. 8 – [d] P_4t-Bu was used as a commercially available solution in hexane – [e] Presence of α-monofluoro-β-ketosulfoxide in small quantities was observed – [f] Hexane from the commercially available solution of P_4t-Bu was removed under reduced pressure and the superbase was solubilized in the desired

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solvent at –30 °C – [8] P_4t-Bu not being soluble in DMF, the reaction mixture was poured onto the superbase suspension in DMF.

A ^{19}F NMR monitoring of the conversion of sulfoxide **4a** over time was conducted with 1 and 2 equivalents of superbase (Figure 1). These two trials were expected to provide information on the quantity of superbase required and on the reaction time needed to achieve full conversion. A total conversion was observed after 5 minutes in both cases. The diastereomeric excesses were also measured on ^{19}F NMR spectra after 5, 15, 45 and 120 minutes. Interestingly, the NMR spectra analyses showed increasing diastereoselectivities over time. When 2 equivalents were used, after 5 minutes, the diastereomeric excess was low (24%). However, a perfect diastereoselectivity was observed after 2 hours of stirring at –30 °C. When one equivalent was used, the diastereoselectivity was much lower after 2 hours (52%).

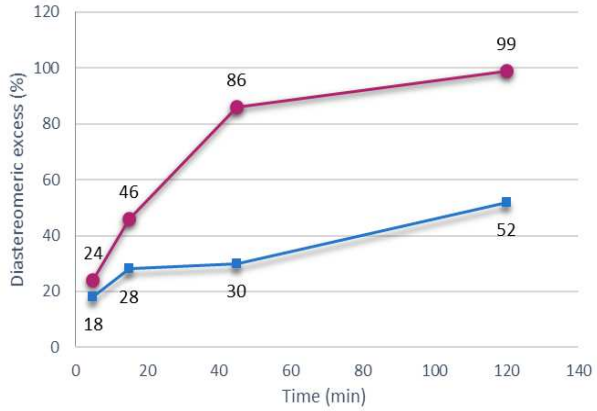


Figure 1. Evolution of the d.e. over time for 1 equivalent (blue curve) or 2 equivalents (pink curve) of P_4t-Bu (^{19}F NMR study)

The evolution of the diastereomeric ratio was then studied at different temperatures in the reaction of **4a** with benzaldehyde, yielding **21a-1** (Figure 2). It was observed that with higher reaction temperatures, perfect diastereoselectivities (d.r. > 99:1) were obtained faster (after 15 minutes at 20 °C and after 2 hours at 0 °C and –30 °C). However, it was also noticed that at a given time, the highest the temperature, the highest the quantity of a side product (Figure 3). For instance, by carrying out the reaction at 20 °C for 15 minutes or at –30 °C for 2 hours, perfect diastereoselectivities were obtained in both cases. However, at 20 °C after 15 minutes, 12% of side product had appeared, while only 5% were measured after 2 hours for the reaction carried out at –30 °C. It was therefore concluded that it is preferable to perform the reaction at low temperature (–30 °C) to minimize the amount of side product (ca. 5%), even if the reaction time required to get full diastereoselectivity is longer (2 hours). This side product was isolated and characterized as the corresponding α-monofluoro-β-ketosulfoxide **22a-1** (see Table 5).

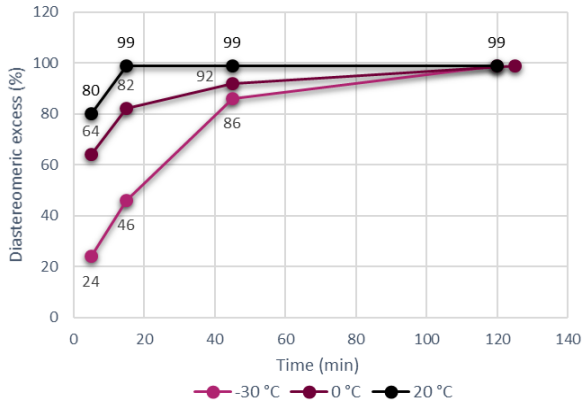


Figure 2. Evolution of the diastereomeric excess over time at different temperatures for 2 equivalents of P_4t-Bu (^{19}F NMR study)

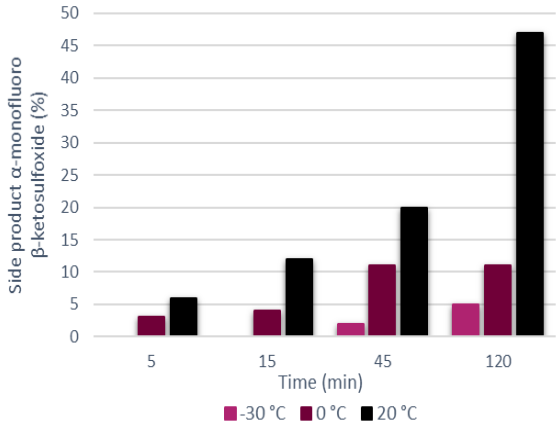
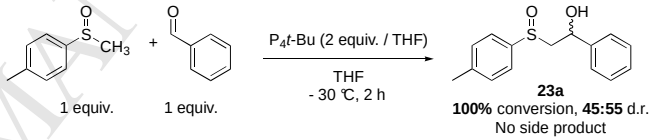


Figure 3. Evolution of the percentage of side products **22a** formed over time at different temperatures for 2 equivalents of P_4t-Bu (^{19}F NMR study)

It is noteworthy that under these optimized conditions, the corresponding non-fluorinated β-hydroxysulfoxide **23a** was obtained with low diastereoselectivity (Scheme 9). This suggests that the two fluorine atoms play an important role in the stereoselectivity of the reaction, for instance by affecting the pKa of the neighbouring protons.



Scheme 9. Access to β-hydroxysulfoxide **23a** with low diastereoselectivity

A screening of different carbonyl derivatives was further performed employing these optimized conditions (Table 5). Several observations already led us to assume that the mechanism of the reaction would involve a kinetic resolution.[8] The first equivalent of the superbase was suspected to deprotonate the difluoromethyl sulfoxide, generating the corresponding carbanion that will further react with the aldehyde. To explain the good diastereoselectivities obtained in some cases, we then assumed that, due to the acidifying effect of the two fluorine atoms, the second equivalent of P_4t-Bu would abstract the proton in α position of the deprotonated alcohol and that only one of the two diastereomers of the newly generated α,α-difluoro-β-hydroxysulfoxide **21** would undergo this process, leading to fluoride elimination. After work up, this would afford the corresponding α-monofluoro-β-ketosulfoxide **22** along with the remaining untouched diastereomer of the α,α-difluoro-β-hydroxysulfoxide **21**.[8]

This mechanism can be supported by several observations. First, the diastereomeric ratio has been shown to evolve over time (Figures 1 and 2), which is in agreement with the potential preferential consumption of one diastereomer with regard to the other. In other words, the enrichment could effectively be explained by the attack undergone by only one of the diastereomeric deprotonated α,α-difluoro-β-hydroxysulfoxides. As observed during the screening of different carbonyl derivatives (Table 5), when diastereomeric ratios are largely in favor of one diastereomer, yields remain moderate (Entries 1 and 9 for instance). In the case of excellent diastereoselectivities, one diastereomer is assumed to be converted into the corresponding α-monofluoro-β-ketosulfoxide. The yields are therefore obviously dependent on the initial proportion of the untouched

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diastereomer of α,α-difluoro-β-hydroxysulfoxide obtained first with low diastereoselectivities. Second, the diastereoselectivities reached starting with ketones are low (Entries 10 and 11). This corroborates with the lack of proton α to oxygen on the generated carbinol, which prevents any stereoenrichment by the assumed deprotonation/fluoride elimination mechanism. Last, high stereoselectivities were observed when P_4t-Bu was used as the base, but not with LiHMDS, KHMDS or *t*-BuOK, which is consistent with the higher basicity of the phosphazene superbase.

Table 5. Screening of different carbonyl derivatives by using P_4t-Bu

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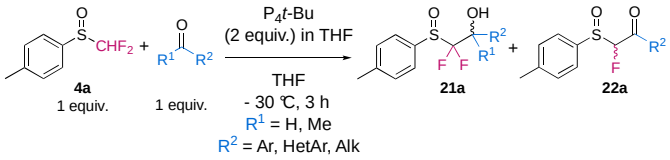


Entry	R^1	R^2	21a Yield – d.r.[b]	Side product 22a (%)[c]
1[a]	Phenyl	H	**21a-1** 53% - 99:1	**22a-1** 20
2	1-Naphthyl	H	**21a-5** 90% - 56:44	**22a-5** 1
3	2-Naphthyl	H	**21a-11** 33% - 73:27	**22a-11** 3
4	2-Pyridinyl	H	**21a-12** 32% - 88:12	**22a-12** 8
5	3-Pyridinyl	H	**21a-6** 77% - 69:31	**22a-6** 2
6	2-Thiophenyl	H	**21a-7** 62% - 70:30	**22a-7** 3
7	3-Thiophenyl	H	**21a-13** 52% - 55:45	**22a-13** 0
8	2-Furyl	H	**21a-8** 96% - 57:43	**22a-8** 0
9	3-Furyl	H	**21a-14** 31% - 98:2	**22a-14** 21
10	-$(CH_2)_2$-Phenyl	Methyl	**21a-10** 89% - 60:40	**22a-10** 0
11	Phenyl	Methyl	**21a-9** 57% - 56:44	**22a-9** 0
12	4-Methoxyphenyl	H	**21a-16** 73% - 79:21	**22a-16** 4

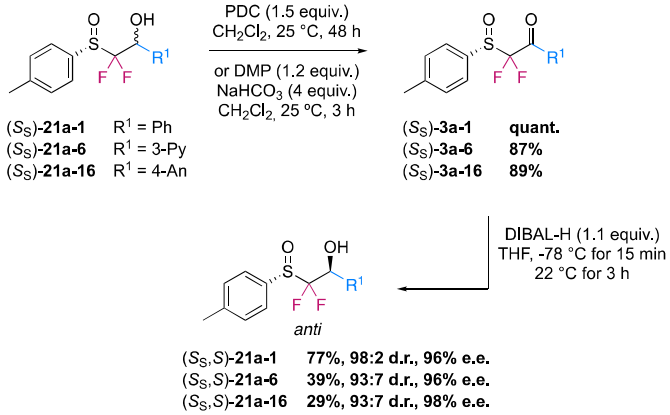
[a] Reaction was carried out for 2 hours – [b] Diastereomeric ratios were determined by ^{19}F NMR spectroscopy – [c] The percentages of α-monofluoro-β-ketosulfoxide **22a** were measured by ^{19}F NMR spectroscopy and confirmed by ^{1}H NMR spectroscopy.

Interestingly, concerning the relative configuration of the α,α-difluoro-β-hydroxysulfoxide **21a**, it appears that for most compounds **21a**, the same trends are observed in terms of ^{19}F NMR signals, where typical data is obtained for the ABX or AB systems. Indeed, when P_4t-Bu is used as the base, (1) the major diastereomer produced (D_{maj}) always shows a much larger $\Delta\nu_{AB}$ than the minor diastereomer (D_{min}); (2) $J_{F\text{-}F} = J_{AB}$ of D_{maj} is always (slightly) inferior to $J_{F\text{-}F} = J_{AB}$ of D_{min}; (3) $J_{H\text{-}F} = J_{AX}$ of D_{maj} is always superior to $J_{H\text{-}F} = J_{AX}$ of D_{min} (which is almost always equal to 0); (4) $J_{H\text{-}F} = J_{BX}$ of D_{maj} is always inferior to $J_{H\text{-}F} = J_{AX}$ of D_{min}.[8] On the other hand, ^{19}F NMR clearly shows that the reversed stereoselectivity is obtained with *t*-BuOK as the base (see ESI). These trends, especially the clearly visible one for $\Delta\nu_{AB}$, are reminiscent of those observed in the case of the parent non-fluorinated β-hydroxysulfoxide,[16b,f] for which the *anti* diastereomer (with regard to the oxygens of the sulfoxide and of the alcohol) has always a larger $\Delta\nu_{AB}$ than the *syn* diastereomer. Accordingly, the method involving the phosphazene superbase would be producing the *anti* isomer as major product, i.e. the (S_S,*S*) diastereomer when starting from the (S_S)-sulfoxide. In fact, this information is infirmed by a crystallographic structure (Figure 4) obtained for the *anti* diastereomer of **21a-1** (*vide infra*), whose $\Delta\nu_{AB}$ corresponds to the one of the minor diastereomer obtained in the superbase method. In other words, the major isomer obtained with the P_4t-Bu superbase is the *syn* diastereomer. This suggests that, in terms of NMR, the two diastereomers behave differently in presence or in absence of the two fluorines atoms, leading to a reversal of the AB(X) system patterns.

2.3. Diastereoselective reduction of α,α-difluoro-β-ketosulfoxides

Solladié and coworkers developed a useful strategy to access highly enantioenriched non-fluorinated alcohols by performing the diastereoselective reduction of enantiopure β-ketosulfoxides in presence of DIBAL-H or by using a combination DIBAL-H/$ZnCl_2$, followed by removal of the chiral auxiliary by desulfinylation with Raney nickel.[16b-g]

With the aim of developing new procedures to synthesize highly enantioenriched α-difluoromethyl alcohols, the former methodology was applied to α,α-difluoro-β-ketosulfoxides (S_S)-**3a-1,6,16** (Scheme 10). These compounds were accessed through oxidation of the previously synthesized α,α-difluoro-β-hydroxysulfoxides (S_S)-**21a-1,6,16** with PDC or DMP. Enantiopure α,α-difluoro-β-ketosulfoxides (S_S)- **3a-1,6,16** were then reduced with DIBAL-H and allowed us to obtain the expected α,α-difluoro-β-hydroxysulfoxides (S_S,*S*)-**21a-1,6,16** with high diastereoselectivity (93:7 to 98:2) and an excellent e.e. (96–98%) of the major diastereomer.[16h]



Scheme 10. Diastereoselective reduction of a α,α-difluoro-β-ketosulfoxides (S_S)-**21a-1,6,16** using DIBAL-H

A X-ray crystallographic structure of the crystallized major diastereomer (S_S,*S*)-**21a-1** was obtained and confirmed that the product of the diastereoselective reduction is the *anti* isomer, as observed in the diastereoselective reduction of non-fluorinated β-ketosulfoxides (Figure 4).[16b, 16f]

This strategy represents an efficient pathway to access to highly enantioenriched α,α-difluoro-β-hydroxysulfoxides of

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opposite relative configuration and α-difluoromethyl alcohols and it is a good alternative to the one previously described.[8]

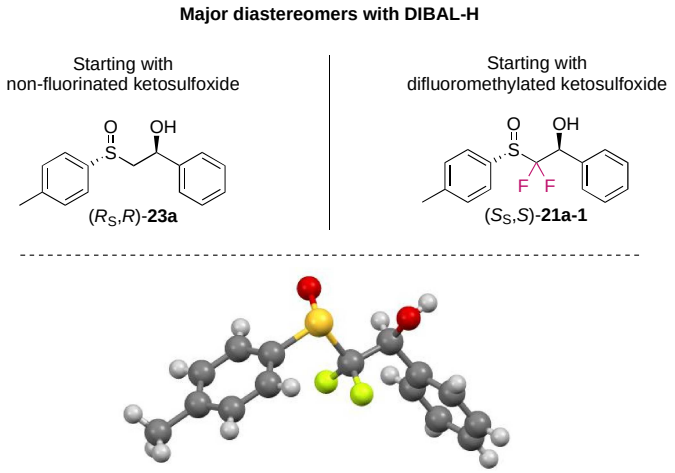
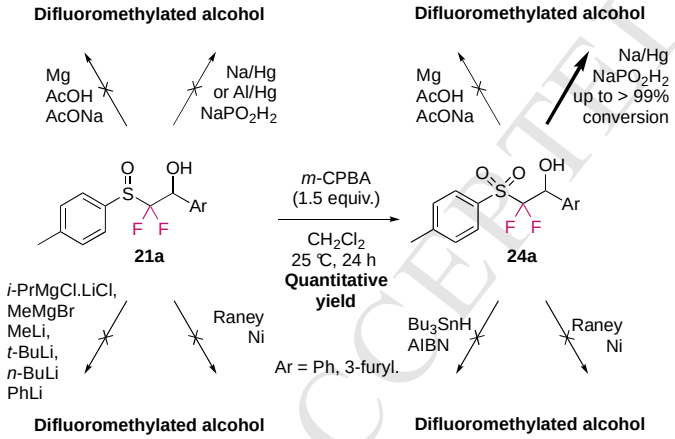


Figure 4. X-ray crystallographic structure of α,α-difluoro-β-hydroxysulfoxide (*S*S,*S*)-**21a-1** comparable to the corresponding non-fluorinated β-hydroxysulfoxide (*R*S,*R*)-**23a** obtained through reduction of β-ketosulfoxide with DIBAL-H. Both have *anti* relative configuration. CCDC 1871933 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

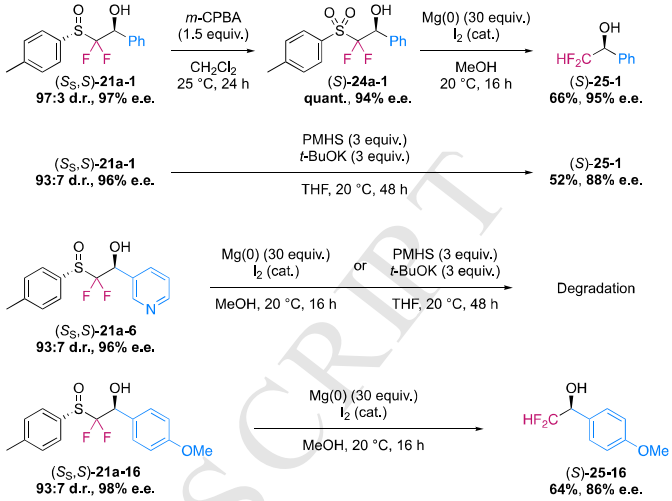
2.4. Removal of the chiral auxiliary to access highly enantioenriched α-difluoromethyl alcohols

Different approaches, among which single electron transfer desulfinylations and well known desulfonylations, that have already been successfully used for the removal of sulfinyl or sulfonyl moieties on non-fluorinated β-hydroxysulfoxides or β-hydroxysulfones have been tested on the previously synthesized fluorinated analogues (Scheme 11).



Scheme 11. Attempts carried out to remove the chiral auxiliary

Unfortunately, Raney nickel gave no conversion of the sulfinyl derivatives nor of the sulfonyl one.[17a-c, 17f, 17g] As we noticed that the reaction involving arenesulfinyl acetate **7b** in presence of organomagnesium (MeMgBr or *i*PrMgCl.LiCl) or organolithiated reagents (MeLi) gave access to the corresponding alkyl aryl sulfoxide by departure of ethyl difluoroacetate anion, it was decided to assess such bases in the desulfinylation of α,α-difluoro-β-hydroxysulfoxide **21a**. Sadly, the chiral auxiliary was not removed in presence of these reagents. Similar results were observed with PhLi or *tert*-BuLi for instance. Reactions of desulfinylation or desulfonylation involving freshly prepared Al/Hg amalgam were not successful on either sulfinyl alcohol **21a** or sulfonyl alcohol **24a** while those carried out in presence of Na/Hg gave good yields but were nevertheless poorly reproducible.[17e] The same conclusions were made in the case of the desulfonylation by using 15 equivalents of magnesium in an acetate buffer.[36a]



Scheme 12. Access to highly enantioenriched α,α-difluoromethylated alcohols (*S*)-**25-1,16** by desulfonylation or desulfinylation

Eventually, the expected highly enantioenriched α,α-difluoromethylated alcohols (*S*)-**25** could be nevertheless obtained by three different routes (Scheme 12). First, after oxidation of a 97:3 d.r. sample of (*S*S,*S*)-**21a-1** to sulfone (*S*)-**24a-1**, the latter was desulfonylated by means of magnesium turnings with catalytic iodine in methanol, yielding (*S*)-**25-1** with perfect retention of the stereoenrichment at carbon all along the process (i.e. from 97:3 d.r. to 95% e.e.). Second, a direct desulfinylation of (*S*S,*S*)-**21a-1** could be carried out by means of poly(methylhydrosiloxane) in the presence of *t*-BuOK,[36c] following a strategy by Midura *et al.*,[36b] modified by using PMHS instead of triphenylsilane. Again, perfect retention of configuration at carbon was obtained (from 93:7 d.r. to 88% e.e.). Third, the direct desulfinylation could also be performed with the magnesium method, as shown with the stereoretentive transformation of (*S*S,*S*)-**21a-16** into (*S*)-**25-16** (from 93:7 d.r. to 86% e.e.). On the other hand, the 3-pyridinyl-substituted compound (*S*S,*S*)-**21a-6** only led to degradation under the two sets of reaction conditions, with generation of numerous unidentified byproducts.

Conclusions

After this study, we managed to address the issue of the synthesis of a highly enantioenriched aryl difluoromethyl sulfoxide and to find a strategy to access to α,α-difluoro-β-hydroxysulfoxides with high diastereoselectivities. The latter can also be synthesized through diastereoselective reduction of the corresponding α,α-difluoro-β-ketosulfoxides. Highly enantioenriched α,α-difluoromethylated alcohols can finally be obtained by desulfonylation of the corresponding α,α-difluoro-β-hydroxysulfones, or simple desulfinylation of highly diastereo- and enantio-enriched α,α-difluoro-β-hydroxysulfoxides by using iodine-activated magnesium or PMHS/*t*-BuOK. Notably, the stereoenrichment at the carbinol carbon atom is perfectly preserved during the whole process.

3. Experimental section

4.0. General experimental methods and equipment

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Starting materials, if commercially available, were purchased from standard suppliers (Sigma-Aldrich, Fluorochem, ABCR, Acros, Alfa Aesar or Apollo scientific) and used as such, provided that adequate checks by NMR analysis had confirmed the claimed purity. When needed, solvents were purified and dried following standard procedures. THF was dried by distillation over sodium/benzophenone prior to use. Toluene, when used anhydrous, was either dried over 4 Å molecular sieves previously activated overnight at 300 °C under vacuum or dried by distillation over sodium. Anhydrous DMF purchased from Sigma Aldrich was used as received. Air- and moisture- sensitive materials were stored and handled under an atmosphere of argon. Reactions were carried out under an atmosphere of argon when needed. Reactions were monitored by using thin-layer chromatography with precoated silica on aluminum foils (0.25 mm, Merck silica-gel (60-F_{254})). Flash column chromatography was performed on VWR silica gel (40–63 μm) using the indicated solvents, the solvent systems being indicated in v/v. When needed, demetalled silica was used. It was prepared by adding an aqueous solution of 2M HCl in silica followed by several washings with water.[37] Butyllithium (1.6 M in hexanes, Aldrich) was used as a solution in hexanes and its concentration was determined following the Wittig-Harborth double titration method ((total base) - (residual base after reaction with 1,2-dibromoethane)).[38] Spectroscopic NMR and MS data were obtained using chromatographically homogeneous samples. ^{1}H NMR (400 or 500 MHz), ^{19}F NMR (376 or 471 MHz) and ^{13}C NMR (101 or 126 MHz) spectra were recorded in $CDCl_3$ on Bruker Avance III HD 400 and 500 MHz instruments respectively. Chemical shifts are reported in parts per million (ppm) and are referred to partially deuterated chloroform ($\delta[^{1}H]$ = 7.26 ppm and $\delta[^{13}C]$ = 77.16 ppm). Multiplicities were abbreviated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), td (triplet of doublets), dd (doublet of doublets) and their corresponding combinations. Coupling constants *J* were given in Hz. Spectra were processed with the program NMR notebook (Version 2.80, NMRtec). IR spectra were recorded on a Perkin Elmer UATR Two spectrometer coupled to a diamond window ATR. Only the more representative frequencies are reported in cm^{-1}. Specific rotations $[\alpha]_D$ were determined at 20 °C on an Anton Paar MCP 200 polarimeter. The concentration (c) is indicated in decagram per liter (dag/L). Chiral HPLC analyses were performed on a Shimadzu Prominence chromatograph. High-resolution mass spectra (HRMS) were recorded with a Bruker MicroTOF mass analyser under ESI in positive ionization mode detection (measurement accuracy ≤ 15 ppm) by the analytical facility at the Université de Strasbourg. The X-ray crystallographic structure analysis was performed by the radio-crystallographic facility at the Université de Strasbourg. The analysis was carried out on a Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N_2 device, using Mo-Kα radiation (λ = 0.71073 Å).

*4.1. General procedure for the obtention of racemic α,α-difluoro-β-sulfanylacetates **6a-e***

A solution of the corresponding thiophenol (1 equiv.) dissolved in anhydrous DMF (2.3 mol/L) was cannulated dropwise onto a suspension of sodium hydride (60% dispersion in mineral oil; 1.1 equiv.) in anhydrous DMF (3 mol/L) at 0 °C under argon. Ethyl bromodifluoroacetate (1 equiv.) was then syringed dropwise into the previous solution. The reaction mixture was heated at 40 °C for the desired time, then cooled to 0 °C, quenched with water and extracted three times with CH_2Cl_2. The combined organic layers were washed with large amounts of water and with a saturated solution of NaCl. The resulting organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Ethyl 2,2-difluoro-2-(*p*-tolylthio)acetate ***6a*** and ethyl 2,2-difluoro-2-(4-chlorophenylthio)acetate **6b** *were described in our previous paper[8] and in the* literature.[39]

Ethyl 2,2-difluoro-2-(phenylthio)acetate **6c**

The reaction mixture was stirred for 21 hours at 40 °C. The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 95/5). Light-yellow oil. 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J* = 7.0 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.43-7.37 (m, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –82.2 (s, 2F). These data are consistent with those already reported in the literature.[40]

Ethyl 2,2-difluoro-2-((4-methoxyphenyl)thio)acetate **6d**

The reaction mixture was stirred for 43 hours at 40 °C. The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 95/5). Light-yellow oil. 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.53 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –83.2 (s, 2F). These data are consistent with those already reported in the literature.[39]

Ethyl 2,2-difluoro-2-(naphthalen-1-ylthio)acetate **6e**

The reaction mixture was stirred for 24 hours at 40 °C. The crude mixture was not purified. Orange oil. 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.55 (d, *J* = 8.6 Hz, 1H), 8.03-7.85 (m, 3H), 7.64 (ddd, *J* = 1.3 Hz, 6.8 Hz, 8.4 Hz, 1H), 7.56 (ddd, *J* = 1.2 Hz, 6.8 Hz, 8.1 Hz, 1H), 7.50 (dd, *J* = 7.3 Hz, 8.2 Hz, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –82.2 (s, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 161.7 (t, *J* = 32.7 Hz), 138.0, 135.9, 134.3, 132.1, 128.6, 127.6, 126.8, 126.1, 125.7, 122.3, 120.2 (t, *J* = 288.1 Hz), 63.6, 13.6. IR *ν* (cm^{-1}) 3058, 2985, 2927, 2855, 1763, 1504, 1371, 1290, 1124, 1099, 1015, 984, 965, 835, 800, 772, 721. HRMS (ESI) calcd for $C_{14}H_{13}F_2O_2S$: 283.0599, found: 283.0619.

*4.2. General procedures for the obtention of racemic α,α-difluoro-β-sulfinylacetates **7a-e***

Procedure A – Oxidation by using periodic acid and $FeCl_3$

The corresponding sulfide **6** (1 equiv.) and $FeCl_3$ (3 mol%) were dissolved in acetonitrile ($3.7x10^{-1}$ mol/L). After 10 minutes of stirring, periodic acid (1 equiv.) was added to the mixture which was mechanically stirred at 25 °C. If necessary, and after controlling the conversion by ^{1}H NMR, periodic acid was added to the reaction mixture according to the proportions required to reach full conversion. After full conversion was obtained, the reaction was slowly quenched with a saturated solution of $Na_2S_2O_3$. The aqueous phase was extracted several times with CH_2Cl_2. The combined organic layers were washed with water and with a saturated solution of NaCl, dried over anhydrous sodium sulfate and concentrated under reduced pressure.

Procedure B – Oxidation by using freshly prepared trifluoroperoxyacetic acid

To a solution of trifluoroperoxyacetic acid (TFPAA) at 0 °C (1 equiv., freshly prepared by mixing 1 equiv. of H_2O_2, 30% w/w in water, with 1 equiv. of trifluoroacetic acid (TFA) at 0 °C) was added dropwise sulfide **6** (1 equiv.) dissolved in TFA (0.6 mol/L). The solution was warmed to 25 °C and stirred at this

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temperature for one day. The reaction mixture was carefully poured onto a saturated solution of $NaHCO_3$. The aqueous phase was extracted three times with AcOEt. The combined organic phases were washed with water and with a saturated solution of NaCl, dried over anhydrous sodium sulfate and concentrated under reduced pressure.

Compounds **7a,b** were synthesized following *procedure A* and were described in our previous paper[8] and in the literature.[19b,39]

Ethyl 2,2-difluoro-2-(phenylsulfinyl)acetate **7c**

Following *procedure A*, the reaction mixture was stirred for 16 hours at 25 °C. The crude was purified by chromatography on demetalated silica gel with cyclohexane/AcOEt (100/0 to 80/20). Yellow oil. 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.73 (d, J = 7.6 Hz, 2H), 7.67-55 (m, 3H), 4.25 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −110.2 (AB system, J_{AB} = 227.5 Hz, $\Delta\nu_{AB}$ = 810.6 Hz, 2F). These data are consistent with those already reported in the literature.[19b]

Ethyl 2,2-difluoro-2-((4-methoxyphenyl)sulfinyl)acetate **7d**

Following *procedure A*, the reaction mixture was stirred for 2 days at 25 °C. The crude was clean enough not to be purified. Yellow oil. Quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.9 Hz, 2H), 4.30 (qd, J = 1.3 Hz, 7.2 Hz, 2H), 3.87 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −111.0 (AB system, J_{AB} = 227.5 Hz, $\Delta\nu_{AB}$ = 749.7 Hz, 2F). These data are consistent with those already reported in the literature.[19b]

Ethyl 2,2-difluoro-2-(naphthalen-1-ylsulfinyl)acetate **7e**

Following *procedure B*, the reaction mixture was stirred for 1 day at 20 °C. The crude was clean enough not to be purified. Brown oil. 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (d, J = 7.3 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.96-7.88 (m, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.59 (m, 2H), 4.05 (qd, J = 2.0 Hz, 7.1 Hz, 2H), 1.10 (t, J = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −108.6 (AB system, J_{AB} = 221.4 Hz, $\Delta\nu_{AB}$ = 498.7 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 159.4 (t, J = 28.2 Hz), 133.7, 133.5, 132.1, 130.6, 128.9, 127.9, 127.1, 126.2, 125.3, 122.2, 118.9 (t, J = 304.2 Hz), 64.1, 13.6. IR ν (cm^{-1}) 3060, 2925, 2855, 1758, 1506, 1371, 1300, 1161, 1142, 1127, 1082, 1011, 966, 956, 855, 802, 769, 711. HRMS (ESI) calcd for $C_{14}H_{12}F_2KO_3S$: 337.0107, found: 337.0103.

*4.3. General procedures for the obtention of racemic difluoromethyl sulfoxides **4a-e***

Procedure C – Under thermal conditions

The corresponding sulfinylacetate **7** (1 equiv.), LiCl (2 equiv.) and H_2O (2 equiv.) were dissolved in DMSO (1.2×10^{-1} mol/L). The reaction mixture was stirred at 110 °C for the desired time, cooled to room temperature and then poured onto ice-cold water. The aqueous layer was saturated with NaCl and then extracted three times with AcOEt. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Procedure D – Under microwave irradiations

To a suspension of LiCl (2 equiv.) and sulfinylacetate **7** (1 equiv.) in NMP (5.9×10^{-2} mol/L) was added H_2O (2 equiv.). The reaction mixture was heated to 100 °C under microwave irradiation for 15 minutes. The dark brown reaction mixture was cooled to room temperature. An aqueous solution of 1M HCl was added to the mixture. The aqueous layer was extracted three times with AcOEt. The combined organic layers were washed three times with ice-cold water and with a cold saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Compounds **4a,b** were synthesized following *procedure C* and were described in our previous paper[8] and/or in the literature.[19b]

((Difluoromethyl)sulfinyl)benzene **4c**

Following *procedure C*, the reaction mixture was stirred for 24 hours at 110 °C. The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 80/20). White solid. 43% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.71 (d, J = 7.3 Hz, 2H), 7.63-7.55 (m, 3H), 6.04 (t, J = 53.3 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –119.2 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 261.6 Hz, $J_{AX} = J_{BX} = J_{H\text{-}F}$ = 55.2 Hz, $\Delta\nu_{AB}$ = 97.3 Hz, 2F). These data are consistent with those already reported in the literature.[15]

1-((Difluoromethyl)sulfinyl)-4-methoxybenzene **4d**

Following *procedure C*, the reaction mixture was stirred for 15 hours at 110 °C. The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 80/20). White solid. 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.64 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 6.00 (t, J = 55.5 Hz, 1H), 3.86 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –119.7 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 261.6 Hz, $J_{AX} = J_{BX} = J_{H\text{-}F}$ = 55.2 Hz, $\Delta\nu_{AB}$ = 73.7 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 163.4, 127.5, 127.1, 120.8 (t, J = 288.4 Hz), 115.1, 55.5. IR ν (cm^{-1}) 3371, 3029, 2974, 2955, 1592, 1572, 1468, 1455, 1438, 1411, 1341, 1310, 1281, 1255, 1175, 1100, 1083, 1037, 1023, 970, 841, 821, 797, 779.

1-((Difluoromethyl)sulfinyl)naphthalene **4e**

Following *procedure D*, the reaction mixture was stirred for 15 minutes at 100 °C under microwave irradiations. The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 70/30). White solid. 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.18 (d, J = 7.2 Hz, 1H), 8.14-8.01 (m, 2H), 7.99-7.91 (m, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.65-7.56 (m, 2H), 6.20 (t, J = 55.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –116.8 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 258.2 Hz, $J_{AX} = J_{BX} = J_{H\text{-}F}$ = 55.9 Hz, $\Delta\nu_{AB}$ = 749.7 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 133.6, 133.2, 132.7, 130.3, 129.1, 128.1, 127.2, 125.5, 125.2, 124.1, 121.9, 121.7 (t, J = 290.8 Hz). IR ν (cm^{-1}) 3059, 2976, 2926, 1505, 1262, 1143, 10,91, 1064, 1053, 1024, 802, 767, 690. HRMS (ESI) calcd for $C_{11}H_9F_2OS$: 227.0337, found: 227.0339.

*4.4. Access to sulfide **12b***

(4-Chlorophenyl)(difluoromethyl)sulfane **12b**

To a suspension of LiCl (2 equiv., 32.8 mg, 750 µmol) and ethyl 2-(4-chlorophenylthio)-2,2-difluoroacetate **6b** (1 equiv., 100 mg, 375 µmol) in 3 mL of NMP was added H_2O (2 equiv., 13.5 µL, 0.75 mmol). The reaction mixture was heated at 200°C under microwave irradiations for 30 minutes, cooled to 25 °C and quenched with a solution of 1M HCl. It was then extracted three times with AcOEt. The combined organic layers were washed with water and a with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel with pentane. 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.81 (t, J = 56.7 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –91.7 (d,

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J = 56.5 Hz, 2F). These data are consistent with those already reported in the literature.[41]

*4.5. Attempts of enantioselective oxidation on sulfide **12b***

See supplementary data for more details concerning procedures and optimization.

1-Chloro-4-((difluoromethyl)sulfonyl)benzene **13b**

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.93 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 6.19 (t, J = 53.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –121.3 (d, J = 53.1 Hz, 2F). These data are consistent with those already reported in the literature.[42]

4.6. Attempted oxidations of L-menthyl sulfanylacetates

(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl 2-[(4-chloro phenyl)sulfanyl]-2,2-difluoroacetate **15b**

To a solution of ethyl 2-(4-chlorophenylthio)-2,2-difluoro acetate **6b** (1 equiv., 1 g, 3.75 mmol) in 8 mL of anhydrous toluene were added L-menthol (5 equiv., 2.93 g, 18.8 mmol), DMAP (2.6 equiv., 1.19 g, 9.75 mmol) and 4 Å molecular sieves (500 mg). The reaction mixture was then heated under reflux for 24 hours, then cooled to 25 °C and filtered. The filtrate was concentrated under reduced pressure. The crude was purified by chromatography on silica gel with *n*-hexane/CH_2Cl_2 (80/20) and **15b** was obtained as a transparent oil. 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 4.77 (td, J = 4.4 Hz, 11.1 Hz, 1H), 1.93 (d, J = 12.0 Hz, 1H), 1.81 (quin, J = 7.0 Hz, 1H), 1.70 (d, J = 12.2 Hz, 2H), 1.47 (t, J = 11.6 Hz, 2H), 1.13-0.94 (m, 2H), 0.91 (dd, J = 7.2 Hz, 9.3 Hz, 6H), 0.89-0.81 (m, 1H), 0.75 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –81.5 (AB system, $J_{AB} = J_{F\text{-}F}$ = 215.9 Hz, $\Delta\nu_{AB}$ = 118.8 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 161.2 (t, J = 31.9 Hz), 137.9, 137.4, 129.7, 123.5, 119.9 (dd, J = 228.3 Hz), 78.8, 46.9, 40.3, 34.1, 31.5, 26.3, 23.5, 22.0, 20.8, 16.3. IR ν (cm^{-1}) 2957, 2928, 2872, 1760, 1575, 1477, 1456, 1390, 1371, 1291, 1283, 1111, 1092, 1006, 980, 947, 908, 845, 823, 747, 724,701. HRMS (ESI) calcd for $C_{18}H_{23}ClF_2O_2S$ (MNa^+): 399.0968, found (MNa^+): 399.0966. $[\alpha]_D^{20}$ = –36.2 ° (c 0.1, EtOH).

(1*R*,2*S*,5*R*)-5-Methyl-2-(propan-2-yl)cyclohexyl 2-[(4-chloro phenyl)sulfinyl]-2,2-difluoroacetate **16b**

Sulfanylester **15b** (1 equiv., 100 mg, 265 µmol) and $FeCl_3{\cdot}6H_2O$ or **18** (resp. 3 or 5 mol%) were dissolved in 0.7 mL of MeCN and stirred at 25 °C for 5 minutes. To this solution was added H_5IO_6 (1.43 equiv., 88.3 mg, 379 µmol). The reaction was then heated at 45 °C for 90 minutes., then quenched with an aqueous saturated solution of $Na_2S_2O_3$ and extracted four times with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was clean enough not to be purified. 87% yield. Transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) *1:1 mixture of two diastereomers* δ (ppm) 7.68 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 4.81 (qd, J = 4.5 Hz, 11.0 Hz, 1H), 1.95 (d, J = 11.7 Hz, 0.5H), 1.87 (d, J = 12.2 Hz, 0.5H), 1.84-1.75 (m, 1H), 1.75-1.65 (m, 2H), 1.53-1.41 (m, 2H), 1.09-0.97 (m, 2H), 0.95-0.85 (m, 7H), 0.75 (d, J = 7.0 Hz, 1.5H), 0.72 (d, J = 7.0 Hz, 1.5H). ^{19}F NMR (376 MHz, $CDCl_3$) *First diastereomer* δ (ppm) −109.8 (AB system, J_{AB} = 227.5 Hz, $\Delta\nu_{AB}$ = 1268 Hz, 1F); *Second diastereomer* δ (ppm) −109.4 (AB system, J_{AB} = 228.9 Hz, $\Delta\nu_{AB}$ = 829 Hz, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) *Two diastereomers* δ (ppm) 159.2 (dd, J = 26.8 Hz, 29.1 Hz), 159.1 (t, J = 27.8 Hz), 140.0, 139.9, 134.7, 129.9, 129.8, 127.8, 117.9 (dd, J = 302.5 Hz, 305.6 Hz), 117.8 (t, J = 304.3 Hz), 79.8, 79.8, 46.7, 40.4, 40.4, 34.0, 33.9, 31.6, 26.2, 26.0, 23.4, 23.3, 22.0, 20.7, 16.2, 16.1. IR ν (cm^{-1}) 2957, 2922, 2872, 1772, 1751, 1576, 1476, 1457, 1392, 1370, 1294, 1169, 1132, 1096, 1083, 1068, 1013, 978, 944, 905, 825, 744, 712. HRMS (ESI) calcd for $C_{18}H_{23}ClF_2KO_3S$: 431.0656, found: 431.0635.

2-[(4-Chlorophenyl)sulfinyl]-2,2-difluoroacetic acid **17b**

To a solution of sulfinylester **16b** (1 equiv., 87.4 mg, 223 µmol) in 0.5 mL of EtOH was added NaOH (1 equiv., 8.9 mg, 223 µmol). The reaction mixture was heated at 40 °C for 17 hours and then cooled to room temperature. Ethanol was removed under reduced pressure. The residue was then dissolved in a minimum amount of water (1 mL) and acidified at 0 °C until pH = 1 by using an aqueous solution of 2M HCl. The aqueous phase was saturated with NaCl and extracted four times with THF. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. 91% yield. White solid. ^{1}H NMR (400 MHz, THF-d_8) δ (ppm) 9.46-8.33 (br s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H). ^{19}F NMR (376 MHz, THF-d_8) δ (ppm) –111.9 (AB system, $J_{AB} = J_{F\text{-}F}$ = 224.8 Hz, $\Delta\nu_{AB}$ = 717.0 Hz, 2F). ^{13}C NMR (101 MHz, THF-d_8) δ (ppm) 161.0 (t, J = 27.0 Hz), 139.6, 137.0, 130.1, 128.5, 119.2 (t, J = 302.5 Hz). IR ν (cm^{-1}) 3096, 2919, 2851, 2646, 2508, 1768, 1572, 1478, 1426, 1395, 1275, 1175, 1139, 1114, 1079, 1035,1010, 947, 887, 827, 772, 745, 702. HRMS (ESI) calcd for $C_8H_5ClF_2NaO_3S$: 276.9508, found: 276.9484.

*4.7. Access to highly enantioenriched difluoromethyl p-tolyl sulfoxide **4a***

For more details concerning its synthesis and analyses (NMR, chiral HPLC, IR, HRMS, etc.), see our previous paper.[8]

4.8. Access to α,α-difluoro-β-hydroxysulfoxides – Starting conditions

Procedure E – Prakash and Hu's optimized conditions

In a vial under argon were dissolved difluoromethyl *p*-tolyl sulfoxide **4a** (1 equiv., 50 mg, 263 µmol) and the carbonyl derivative (2 equiv., 526 µmol) in 1 mL of freshly distilled THF. The mixture was stirred at –30 °C for 5 minutes. Potassium *tert*-butoxide (2 equiv., 60 mg, 526 µmol), previously solubilised in 1 mL of freshly distilled THF, was added dropwise to the previous solution. The reaction mixture was stirred at –30 °C for 40 minutes, then quenched with water at –30 °C. The aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NH_4Cl and with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Compounds **21a-1,5–16** were synthesized following *procedure E* and were described in our previous paper.[8]

2,2-Difluoro-1-(*p*-tolyl)-2-(*p*-tolylsulfinyl)ethan-1-ol **21a-2**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 50/50). 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) *Two diastereomers* δ (ppm) 7.60 (d, J = 7.5 Hz, 2H), 7.40 (d, J = 8.0 Hz, 0.8H), 7.38-7.32 (m, 3.2H), 7.20 (d, J = 8.0 Hz, 0.8H), 7.17 (d, J = 8.0 Hz, 1.2H), 5.39 (dd, J = 3.1 Hz, 22.8 Hz, 0.6H), 5.30 (ddd, J = 2.8 Hz, 3.7 Hz, 10.3 Hz, 0.4H), 4.79 (d, J = 5.3 Hz, 0.6H), 3.92 (d, J = 3.8 Hz, 0.4H), 2.43 (s, 1.2H), 2.42 (s, 1.8H), 2.36 (s, 1.2H), 2.34 (s, 1.8H). ^{19}F NMR (376 MHz, $CDCl_3$) *First diastereomer* δ (ppm) –115.0 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 218.0 Hz, $J_{AX} = J_{H\text{-}F}$ = 10.2 Hz, $J_{BX} = J_{H\text{-}F}$ = 15.0 Hz, $\Delta\nu_{AB}$ = 3498 Hz, 0.6F); *Second diastereomer* δ (ppm) –114.1 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 224.8 Hz, $J_{BX} = J_{H\text{-}F}$ = 22.5 Hz, $\Delta\nu_{AB}$ = 2288 Hz, 0.4F). ^{13}C NMR (126 MHz, $CDCl_3$) *Two diastereomers* δ (ppm) 143.6,

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143.5, 139.4, 139.0, 132.8 (d, J = 3.2 Hz), 132.2 (d, J = 3.2 Hz), 131.9, 131.5 (d, J = 1.8 Hz), 130.0, 129.9, 129.3, 129.1, 128.1, 127.9, 126.5, 124.7 (dd, J = 297.0 Hz, 305.2 Hz), 124.0 (dd, J = 293.8 Hz, 309.3 Hz), 73.0 (t, J = 21.8 Hz), 70.4 (dd, J = 19.5 Hz, 29.1 Hz), 21.7, 21.7, 21.4, 21.3. IR ν (cm^{-1}) 3325, 2923, 2855, 1597, 1515, 1494, 1449, 1181, 1112, 1085, 1041, 1015, 975, 835, 810, 780, 747, 703. HRMS (ESI) calcd for $C_{16}H_{17}F_2O_2S$: 311.0912, found: 311.0901.

1-(4-Bromophenyl)-2,2-difluoro-2-(*p*-tolylsulfinyl)ethan-1-ol **21-a3**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 50/50). 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) *Two diastereomers* δ (ppm) 7.62-7.64 (m, 4H), 7.51 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.42-7.30 (m, 8H), 5.47-5.29 (m, 2H), 5.26 (d, J = 5.1 Hz, 1H), 4.25 (d, J = 3.0 Hz, 1H), 2.44 (s, 3H), 2.43 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) *First diastereomer* δ (ppm) –114.5 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 219.3 Hz, $J_{AX} = J_{H\text{-}F}$ = 8.9 Hz, $J_{BX} = J_{H\text{-}F}$ = 15.0 Hz, $\Delta\nu_{AB}$ = 4081 Hz, 0.5F); *Second diastereomer* δ (ppm) –114.1 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 224.8 Hz, $J_{BX} = J_{H\text{-}F}$ = 23.2 Hz, $\Delta\nu_{AB}$ = 2318 Hz, 0.5F). ^{13}C NMR (126 MHz, $CDCl_3$) *Two diastereomers* δ (ppm) 144.0, 143.8, 133.9, 133.3, 133.3, 132.3, 132.3, 131.8, 131.6, 130.1, 129.9, 129.6, 126.5, 126.5, 124.3 (dd, J = 297.0 Hz, 304.7 Hz), 123.8, 123.4, 123.1 (dd, J = 293.4 Hz, 312.0 Hz), 73.0 (t, J = 22.3 Hz), 70.2 (dd, J = 20 Hz, 28.6 Hz), 21.8, 21.7. IR ν (cm^{-1}) 3309, 2921, 1595, 1489, 1403, 1192, 1111, 1084, 1042, 1012, 979, 847, 809, 771, 703. HRMS (ESI) calcd for $C_{15}H_{14}BrF_2O_2S$: 374.9860, found: 374.9853.

1-(2,3-Dimethoxyphenyl)-2,2-difluoro-2-(*p*-tolylsulfinyl)ethan-1-ol **21a-4**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 50/50). 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) *Two diastereomers* δ (ppm) 7.68 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1.1H), 7.39-7.30 (m, 2H), 7.11 (d, J = 7.9 Hz, 0.54H), 7.07-7.01 (m, 1H), 6.98 (d, J = 7.4 Hz, 0.46H), 6.93-6.86 (m, 1H), 5.79 (dd, J = 6.0 Hz, 24.6 Hz, 0.54H), 5.36 (dt, J = 6.1 Hz, 19.5 Hz, 0.46H), 4.98 (d, J = 6.6 Hz, 0.54H), 4.63 (d, J = 6.6 Hz, 0.46H), 3.85 (s, 1.4H), 3.83 (s, 1.4H), 3.81 (s, 1.6H), 3.77 (s, 1.6H), 2.42 (s, 1.4H), 2.41 (s, 1.6H). ^{19}F NMR (376 MHz, $CDCl_3$) *First diastereomer* δ (ppm) –114.7 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 217.3 Hz, $J_{AX} = J_{H\text{-}F}$ = 6.1 Hz, $J_{BX} = J_{H\text{-}F}$ = 19.8 Hz, $\Delta\nu_{AB}$ = 3764 Hz, 0.46F); *Second diastereomer* δ (ppm) –114.2 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 223.4 Hz, $J_{BX} = J_{H\text{-}F}$ = 24.5 Hz, $\Delta\nu_{AB}$ = 2481 Hz, 0.54F). ^{13}C NMR (126 MHz, $CDCl_3$) *Two diastereomers* δ (ppm) 152.5, 152.4, 147.9, 147.8, 143.6, 143.4, 133.6 (d, J = 3.2 Hz), 133.0 (d, J = 2.3 Hz), 130.0, 129.9, 127.7, 127.2, 126.6, 126.5, 124.7 (dd, J = 297.0 Hz, 306.1 Hz), 124.5 (dd, J = 297.0 Hz, 305.2 Hz), 124.2, 124.1, 121.3, 121.2, 113.5, 113.3, 70.1 (dd, J = 20.9 Hz, 25.0 Hz), 67.1 (dd, J = 19.5 Hz, 28.6 Hz), 61.3, 61.1, 55.9, 55.9, 21.7, 21.7. IR ν (cm^{-1}) 3333, 2941, 1589, 1483, 1432, 1266, 1224,1171, 1116, 1086, 1050, 1005, 977, 898, 810,774, 751, 722. HRMS (ESI) calcd for $C_{17}H_{19}F_2O_4S$: 357.0967, found: 357.0970.

4.9. Optimization attempts for the diastereoselective access to α,α-difluoro-β-hydroxysulfoxides

4.9.1. Addition of chelating agents

Procedure F – Use of $TiCl_4$

To a solution of difluoromethyl *p*-tolyl sulfoxide **4a** (1 equiv., 30 mg, 158 µmol) and 1-naphthaldehyde (2 equiv., 45.1 µL, 315 µmol) in 1 mL of freshly distilled THF at –30 °C was added potassium *tert*-butoxide (2 equiv., 36.1 mg, 315 µmol) previously dissolved in 1 mL of freshly distilled THF, under an atmosphere of argon. Titanium(IV) chloride (2 equiv., 35 µL, 315 µmol) was then added to the reaction mixture. It became dark red. The reaction was stirred at –20 °C for 35 minutes. It was quenched with water and the aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NH_4Cl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Procedure G – Use of $ZnCl_2$

Pre-drying of zinc(II) chloride – $ZnCl_2$ (2 equiv., 71.7 mg, 526 µmol), a highly hygroscopic compound, was previously dried using the following method: in a Schlenk tube, zinc dichloride was heated to 140 °C under vacuum. After 6 hours of stirring under such conditions, the tube was cooled to room temperature and 1 mL of freshly distilled THF was added under an atmosphere of argon. The mixture was stirred until total dissolution of $ZnCl_2$.

Difluoromethyl *p*-tolyl sulfoxide **4a** (1 equiv., 50 mg, 263 µmol) and 1-naphthaldehyde (2 equiv., 71.4 µL, 526 µmol) were introduced in another Schlenk tube. The mixture was cooled to –30 °C and a solution of potassium *tert*-butoxide (2 equiv., 60.2 mg, 526 µmol) dissolved in 1.5 mL of freshly distilled THF was added dropwise, under an atmosphere of argon. The reaction mixture turned dark yellow/orange. The freshly prepared solution of $ZnCl_2$ in THF was then cannulated onto this mixture, which became immediately light-yellow. The reaction was stirred at –30 °C for 35 minutes. It was quenched with water and the aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NH_4Cl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Procedure H – Use of a tetra-substituted 18-crown-6 crown ether

Difluoromethyl *p*-tolyl sulfoxide **4a** (1 equiv., 30 mg, 158 µmol), 1-naphthaldehyde (2 equiv., 45.1 µL, 315 µmol) and crown ether (+)-(2*R*,3*R*,11*R*,12*R*)-1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3,11,12-tetracarboxylic acid (10 mol%, 7.1 mg, 15.8 µmol) were dissolved in 1 mL of freshly distilled THF. The mixture was cooled to –30 °C and potassium *tert*-butoxide (2 equiv., 35.4 mg, 315 µmol) dissolved in 1.5 mL of freshly distilled THF was added dropwise. The reaction mixture was stirred at –30 °C for 35 minutes. It was quenched with water and the aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NH_4Cl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

4.9.2. Varying the aromatic ring of the sulfoxide

Procedure E was used to access α,α-difluoro-β-hydroxysulfoxides **21b-1** to **21e-1**.

2-((4-Chlorophenyl)sulfinyl)-2,2-difluoro-1-phenylethan-1-ol **21b-1**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 80/20). 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *Two diastereomers* δ (ppm) 7.61 (d, J = 8.1 Hz, 2H), 7.53-7.49 (m, 4H), 7.43-7.33 (m, 3H), 5.45 (d, J = 23.0 Hz, 0.5H), 5.33-5.19 (m, 1H), 4.41 (s, 0.5H). ^{19}F NMR (471 MHz, $CDCl_3$) *First diastereomer* δ (ppm) –114.2 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 217.3 Hz, $J_{AX} = J_{H\text{-}F}$ = 10.9 Hz, $J_{BX} = J_{H\text{-}F}$ = 14.3 Hz, $\Delta\nu_{AB}$ = 2764 Hz, 0.48F); *Second diastereomer* δ (ppm) –113.9 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 222.1 Hz, $J_{BX} = J_{H\text{-}F}$ = 22.5 Hz, $\Delta\nu_{AB}$ = 2018 Hz, 0.52F). ^{13}C NMR (101 MHz, $CDCl_3$) *Two diastereomers* δ (ppm) 139.3, 139.2, 134.6, 134.5 (d, J = 2.6 Hz),

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134.2 (d, *J* = 2.2 Hz), 133.8, 129.6, 129.6, 129.5, 129.2, 128.7, 128.5, 128.1, 127.9, 127.9, 127.9, 127.1, 125.2 (dd, *J* = 300.0 Hz, 306.6 Hz), 124.3 (dd, *J* = 295.5 Hz, 309.2 Hz), 72.9 (t, *J* = 22.0 Hz), 70.1 (dd, *J* = 19.4 Hz, 29.3 Hz). IR *ν* (cm^{-1}) 3325, 2920, 2851, 1576, 1494, 1476, 1456, 1393, 1191, 1110, 1093,1079, 1046, 1011, 973, 821, 800, 743, 726, 697. HRMS (ESI) calcd for $C_{14}H_{12}ClF_2O_2S$: 317.0209, found: 317.0192.

2,2-Difluoro-1-phenyl-2-(phenylsulfinyl)ethan-1-ol **21c-1**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 50/50). Quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) *Two diastereomers* *δ* (ppm) 7.77-7.70 (m, 2H), 7.64-7.50 (m, 3.8H), 7.49-7.44 (m, 1.2H), 7.43-7.34 (m, 3H), 5.48-5.35 (m, 1H), 4.40 (d, *J* = 5.3 Hz, 0.6H), 3.69 (d, *J* = 3.9 Hz, 0.4H). ^{19}F NMR (376 MHz, $CDCl_3$) *First diastereomer* *δ* (ppm) –114.2 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 219.3 Hz, $J_{AX} = J_{H\text{-}F}$ = 8.9 Hz, $J_{BX} = J_{H\text{-}F}$ = 15.7 Hz, $\Delta\nu_{AB}$ = 3961 Hz, 0.36F); *Second diastereomer* *δ* (ppm) –113.5 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 224.8 Hz, $J_{BX} = J_{H\text{-}F}$ = 22.5 Hz, $\Delta\nu_{AB}$ = 2495 Hz, 0.64F). These data are consistent with those already reported in the literature.[15]

2,2-Difluoro-2-((4-methoxyphenyl)sulfinyl)-1-phenylethan-1-ol **21d-1**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 50/50). 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *Two diastereomers* *δ* (ppm) 7.65 (d, *J* = 7.8 Hz, 2H), 7.53-7.45 (m, 2H), 7.41-7.33 (m, 3H), 7.06-7.01 (m, 2H), 5.44 (dd, *J* = 1.4 Hz, 22.6 Hz, 0.55H), 5.32 (dd, *J* = 9.6 Hz, 15.3 Hz, 0.45H), 3.86 (s, 1.45H), 3.85 (s, 1.55H). ^{19}F NMR (471 MHz, $CDCl_3$) *First diastereomer* *δ* (ppm) –115.2 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 219.3 Hz, $J_{AX} = J_{H\text{-}F}$ = 9.5 Hz, $J_{BX} = J_{H\text{-}F}$ = 15.6 Hz, $\Delta\nu_{AB}$ = 4746 Hz, 0.45F); *Second diastereomer* *δ* (ppm) –114.4 (ABX system, $J_{AB} = J_{F\text{-}F}$ = 224.5 Hz, $J_{BX} = J_{H\text{-}F}$ = 22.5 Hz, $\Delta\nu_{AB}$ = 2486 Hz, 0.55F). ^{13}C NMR (126 MHz, $CDCl_3$) *Two diastereomers* *δ* (ppm) 163.5, 163.5, 134.9, 134.5 (d, *J* = 1.4 Hz), 129.5, 129.1, 128.6, 128.6, 128.6, 128.4, 128.2, 128.1, 126.6 (d, *J* = 3.2 Hz), 126.0 (d, *J* = 2.3 Hz), 124.5 (dd, *J* = 296.6 Hz, 304.7 Hz), 123.6 (dd, *J* = 292.9 Hz, 309.7 Hz), 114.9, 114.9, 73.4 (t, *J* = 22.3 Hz), 70.6 (dd, *J* = 20.0 Hz, 29.1 Hz), 55.7, 55.7. IR *ν* (cm^{-1}) 3324, 2921, 2817, 1594, 1577, 1496, 1456, 1443, 1308, 1258, 1175, 1108, 1087, 1062, 1027, 978, 831, 798, 729, 699. HRMS (ESI) calcd for $C_{15}H_{14}F_2NaO_3S$: 335.0524, found: 335.0519.

2,2-Difluoro-2-(naphthalen-1-ylsulfinyl)-1-phenylethan-1-ol **21e-1**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 50/50). Quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) *Two diastereomers* *δ* (ppm) 8.21 (d, *J* = 6.5 Hz, 1H), 8.13 (d, *J* = 4.3 Hz, 0.6H), 8.04 (t, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 7.1 Hz, 0.4H), 7.94-7.88 (m, 1H), 7.70-7.63 (m, 1H), 7.59-7.58 (m, 4H), 7.43-7.31 (m, 3H), 5.61 (d, *J* = 19.3 Hz, 0.6H), 5.44 (dd, *J* = 9.5 Hz, 13.3 Hz, 0.4H), 5.28 (br s, 0.6H), 4.33 (br s, 0.4H). ^{19}F NMR (471 MHz, $CDCl_3$) *First diastereomer* *δ* (ppm) −112.0 (ABX system, J_{AB} = 215.9 Hz, $J_{BX} = J_{H\text{-}F}$ = 14.3 Hz, $\Delta\nu_{AB}$ = 4236 Hz, 0.4F). *Second diastereomer* *δ* (ppm) –111.9 (AB system, J_{AB} = 220.7 Hz, $\Delta\nu_{AB}$ = 1588 Hz, 0.6F). ^{13}C NMR (126 MHz, $CDCl_3$) *Two diastereomers* *δ* (ppm) 134.8, 134.4, 133.6, 133.5, 133.2, 133.1, 132.3, 131.2, 130.9, 129.5, 129.1, 128.8, 128.7 128.6, 128.4, 128.2, 128.0, 127.7, 127.6, 127.1, 126.9, 126.8, 126.6, 126.5, 125.5, 125.3, 122.6, 122.5, 73.7 (t, *J* = 22.3 Hz), 70.7 (dd, *J* = 19.1 Hz, 28.2 Hz). IR *ν* (cm^{-1}) 3339, 3063, 2927, 1505, 1455, 1193, 1115, 1064, 1049, 973, 800, 769, 729, 698. HRMS (ESI) calcd for $C_{18}H_{15}F_2O_2S$: 333.0755, found: 333.0748.

4.9.3. Screening of different bases

Procedure I – Use of KHMDS/crown ether 18-crown-6

Pre-drying of crown ether 18-crown-6 – Each time it was used, crown ether 18-crown-6 was previously dried. It was solubilized in anhydrous toluene and the potential traces of water were removed by evaporation of the toluene/water azeotrope under reduced pressure. This procedure was repeated several times and the solid obtained was maintained under vacuum overnight. It is also possible to recrystallize it from acetonitrile.

In a reaction tube under argon were dissolved difluoromethyl *p*-tolyl sulfoxide **4a** (1 equiv., 30 mg, 158 µmmol), benzaldehyde (1 equiv., 16.3 µL, 158 µmol) and, when required, crown ether 18-crown-6 (1 equiv., 41.7 mg, 158 µmol) in 2 mL of the desired anhydrous solvent. The mixture was stirred at –30 °C for 10 minutes. A solution of KHMDS (2 equiv., 0.5 M in toluene, 631 µL, 315 µmol) was then added dropwise to the previous solution at –30 °C. The reaction was stirred at this temperature for the desired time, possibly followed by a period of stirring at room temperature, depending on the result of the TLC control. It was quenched with water and the aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NH_4Cl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Procedure J – Use of LiHMDS/crown ether 12-crown-4

In a reaction tube under argon were dissolved difluoromethyl *p*-tolyl sulfoxide **4a** (1 equiv., 30 mg, 158 µmol), benzaldehyde (1 equiv., 16.3 µL, 158 µmol) and, when required, 12-crown-4 (1 equiv., 27.8 mg, 158 µmol) in 1 mL of the chosen anhydrous solvent. The mixture was stirred at –30 °C for 10 minutes. In the meanwhile, to a solution of distilled HMDS (2 equiv., 67 µL, 315 µmol) in 1.5 mL of the chosen anhydrous solvent at –78 °C was added dropwise *n*-butyllithium (2 equiv., 1.54 M in hexanes, 205 µL, 315 µmol). This solution was stirred at –30 °C for 20 minutes. The mixture was added dropwise to the previous solution. The reaction mixture was stirred at –30 °C for the desired time, possibly followed by a period of stirring at room temperature, depending on the result of the TLC control. It was quenched with water and the aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NH_4Cl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Procedure K – Use of NaH

In a reaction tube under argon were dissolved difluoromethyl *p*-tolyl sulfoxide **4a** (1 equiv., 50 mg, 260 µmol) and benzaldehyde (1 equiv., 50 µL, 260 µmol) in freshly distilled THF. After some minutes of stirring at –78 °C, NaH (2 equiv., 21 mg, 530 µmol, 60% dispersion in oil) was added portionwise. The solution turned yellow then orange. This solution was stirred at this temperature for 2 h and was then allowed to warm to room temperature. It was stirred at this temperature for 1 h. The reaction mixture was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Procedure L-1 – Use of P_4*t*-Bu

Non-reproducible results

In a reaction tube under argon were dissolved difluoromethyl *p*-tolyl sulfoxide **4a** (1 equiv., 15 mg, 78.9 µmol) and benzaldehyde (1 equiv., 8.13 µL, 78.9 µmol) in 1 mL of the

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appropriate anhydrous solvent. P_4t-Bu (0.8 M solution in hexane, 2 equiv., 197 µL, 158 µmol) was added dropwise to this solution cooled to –30 °C. The reaction mixture was stirred at –30 °C for 2 hours, then quenched with water at this temperature. The aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

Procedure L-2 – Use of P_4t-Bu

Reproducible results

Hexane was removed under vacuum from 197 µL of the commercially available solution of P_4t-Bu superbase (0.8 M in hexane, 2 equiv., 197 µL, 158 µmol). The solid obtained was dissolved in 0.7 mL of freshly distilled THF (or another solvent for tests) previously cooled to –30 °C. To a solution of difluoromethyl *p*-tolyl sulfoxide **4a** (1 equiv., 15 mg, 78.9 µmol) and carbonyl derivative (1 equiv., 78.9 µmol) dissolved in 1.8 mL of freshly distilled THF (or another solvent for tests) at –30 °C was added dropwise the previous solution of P_4t-Bu in THF (or another solvent for tests). The reaction mixture was stirred at –30 °C for 2 hours, then quenched with water at this temperature. The aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

4.10. Study with P_4t-Bu

4.10.1. Evolution of the d.r. depending on the stoichiometry in P_4t-Bu

Procedure L-2 was used, varying the stoichiometry in P_4t-Bu (1 or 2 equiv.). After 5, 15, 45 and 120 minutes, 0.5 mL of the reaction mixture were sampled and directly quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with Et_2O and ^{19}F NMR analyses of the different crude mixtures were carried out to determine the conversions and the diastereomeric ratios.

*4.10.2. Evolution of the d.r. and of the percentage of side-product **22a** depending on the temperature*

Procedure L-2 was also used, varying the temperature (–30 °C, 0 °C or 20 °C).

*4.10.3. Synthesis of β-hydroxysulfoxide **23a***

The synthesis of β-hydroxysulfoxide **23a** was carried out by using *procedure L-2*. Methyl *p*-tolyl sulfoxide was employed instead of difluoromethyl *p*-tolyl sulfoxide **4a**.

4.10.4. Screening of different carbonyl derivatives

Procedure L-2 was used for the screening of different carbonyl derivatives. This study and the analyses corresponding to the α,α-difluoro-β-hydroxysulfoxides synthesized is available in the corpus and electronic supporting information of our previous paper.[8]

*4.11. Diastereoselective reduction of α,α-difluoro-β-ketosulfoxides (S_S)-**3a–c***

*4.11.1. General procedures to access to enantiopure α,α-difluoro-β-ketosulfoxides (S_S)-**3a-1,6,16***

Procedure M – Use of PDC as oxidizing agent

4Å molecular sieves and PDC (1.5 equiv.) were added to a solution of 2,2-difluoro-1-aryl-2-(*p*-tolylsulfinyl)ethan-1-ol **21a-1** or **21a-16** in anhydrous CH_2Cl_2. The resulting suspension was stirred at room temperature for 48 h. Et_2O and water were added to the reaction mixture, which was then filtered. The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

(*S*)-2,2-Difluoro-1-phenyl-2-(*p*-toluenesulfinyl)ethan-1-one (S_S)-**3a-1**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 50/50). Quantitative yield. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.01 (dd, J = 1.1 Hz, 8.6 Hz, 2H), 7.67 (tt, J = 1.2 Hz, 7.5 Hz, 1H), 7.56-7.48 (m, 4H), 7.31 (d, J = 7.9 Hz, 2H), 2.42 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) –103.7 (AB system, J_{AB} = $J_{F\text{-}F}$ = 237.7 Hz, $\Delta\nu_{AB}$ = 1223.8 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 185.5 (t, J = 22.7 Hz), 144.1, 135.3, 132.8, 132.5, 130.7, 130.2, 129.0, 126.4, 21.8. IR (cm^{-1}) 2924, 1694, 1597, 1493, 1450, 1274, 1142, 1090, 1067, 974, 810. HRMS (ESI) calcd for $C_{15}H_{13}F_2O_2S$: 295.0598, found: 295.0584.

(*S*)-2,2-Difluoro-1-(4-methoxyphenyl)-2-(*p*-toluenesulfinyl)-ethan-1-one (S_S)-**3a-16**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 80/20). 89% yield. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H), 2.42 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) –104.9 (AB system, J_{AB} = $J_{F\text{-}F}$ = 235.8 Hz, $\Delta\nu_{AB}$ = 1385 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 183.3, 165.4, 143.9, 133.4, 132.9, 130.1, 126.3, 114.2, 55.8, 21.8. IR (cm^{-1}) 2924, 1694, 1597, 1493, 1450, 1274, 1142, 1090, 1067, 974, 810. HRMS (ESI) calcd for $C_{15}H_{13}F_2O_2S$: 295.0598, found: 295.0584. IR (cm^{-1}) 1684, 1598, 1269, 1147, 603. HRMS (ESI) calcd for $C_{16}H_{14}F_2O_3SK$: 363.0263, found: 363.0253.

Procedure N – Use of DMP as oxidizing agent

DMP (1.2 equiv., 685 mg, 0.50 mL, 1.61 mmol) was added to a solution of …(1 equiv., 400 mg, 1.35 mmol) **21a-6** and $NaHCO_3$ (4 equiv., 452.1 mg, 5.38 mmol) in 8 mL of anhydrous CH_2Cl_2 at 25 ºC. The mixture was stirred for 30 min. A saturated solution of $NaHCO_3$ was added to the reaction mixture. The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 30/70). 83% yield.

(*S*)-2,2-Difluoro-1-(3-pyridinyl)-2-(*p*-toluenesulfinyl)-ethan-1-one (S_S)-**3a-6**

The crude was purified by chromatography on demetalled silica gel with cyclohexane/AcOEt (100/0 to 20/80). 87% yield. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.12 (dd, J = 2.3, 1.0 Hz, 1H), 8.84 (dd, J = 4.9, 1.7 Hz, 1H), 8.31 (dq, J = 9.0, 1.9 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.45 (ddd, J = 8.1, 4.8, 0.9 Hz, 1H), 7.36 – 7.30 (m, 2H), 2.42 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) –104.3 (AB system, J_{AB} = $J_{F\text{-}F}$ = 238.4 Hz, $\Delta\nu_{AB}$ = 1907,6 Hz, 2F).^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 185.1 (t, J = 24.6 Hz), 154.9, 151.5, 144.4, 138.0, 132.3, 130.3, 129.8, 128.6, 126.1, 123.6, 21.8. IR (cm^{-1}), 2924, 1699, 1585, 1140, 1089, 810, 700, 515. HRMS (ESI) calcd for $C_{14}H_{11}F_2O_2SNNa$: 318.0371, found: 318.0360.

IR (cm^{-1}) 1699, 1585, 1140, 1089, 810, 700, 515. HRMS (ESI) calcd for $C_{14}H_{11}F_2O_2SNNa$: 318.0371, found: 318.0360.

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*4.11.2. General procedure to access to highly diastereo- and enantioenriched α,α-difluoro-β-hydroxysulfoxides (S_S,S)-**21a-1,6,16** by reduction with DIBAL-H*

A solution of DIBAL-H (1.1 equiv., 1 M in THF,) was added to a solution of enantioenriched (*S*)-2,2-difluoro-1-(het)aryl-2-(*p*-toluenesulfinyl)ethan-1-one (S_S)-**3a** (1 equiv.) in freshly distilled THF (ca. 5 mL /mmol) under argon at –78°C. The resulting mixture was stirred at –78°C for 15 minutes. It was then allowed to warm to 22 ºC and stirred at this temperature for 3 hours. The mixture was cooled to 0 ºC and diluted with Et_2O. Water was slowly added, followed by a 1M solution of NaOH. The cooling bath was removed, and the mixture was stirred for 15 minutes at 22 ºC. The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

(*S*)-2,2-Difluoro-1-phenyl-2-((*S*)-*p*-tolylsulfinyl)ethan-1-ol (S_S,*S*)-**21a-1**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 50/50). 77% yield. 98:2 d.r., 96% e.e. *One diastereomer* ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J* = 7.9 Hz, 2H), 7.49-7.45 (m, 2H), 7.39-7.34 (m, 5H), 5.42 (ddd, *J* = 1.4 Hz, 5.0 Hz, 22.6 Hz, 1H), 4.67 (d, *J* = 5.5 Hz, 1H), 2.43 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) –114.7 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 225.4 Hz, J_{BX} = $J_{H\text{-}F}$ = 22.5 Hz, $\Delta\nu_{AB}$ = 2417 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 143.6, 134.7, 132.3, 130.1, 129.2, 128.5, 128.0, 126.5, 124.4 (dd, *J* = 297.5 Hz, 305.6 Hz), 70.9 (dd, *J* = 20.0 Hz, 28.6 Hz), 21.7. The diastereomeric ratio and the enantiomeric excess of the product were determined by HPLC using a Chiracel IC column (*n*-hexane/*i*-PrOH= 80/20, flow rate 0.5 mL/min, λ = 205 nm, τ = 9.4 min, 10.8 min, 20.0 min, 23.6 min). [α_{589}] = +125.07 (20 °C, 0.895 g/100 mL, $CHCl_3$). IR (cm^{-1}) 3225, 2924, 1494, 1456, 1112, 1086, 1042, 809, 729, 698.

(*S*)-2,2-Difluoro-1-(3-pyridinyl)-2-((*S*)-*p*-tolylsulfinyl)ethan-1-ol (S_S,*S*)-**21a-6**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 30/70). 39% yield. 93:7 d.r., 96% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.66 (s, 2H), 7.89 (d, *J* = 6.8 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 3H), 5.51 (d, *J* = 22.9 Hz, 1H), 2.41 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –114.4 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 225.4 Hz, J_{BX} = $J_{H\text{-}F}$ = 23.2 Hz, $\Delta\nu_{AB}$ = 2245 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 149.9, 148.9, 143.8, 136.2, 132.0 (d, *J* = 3.7 Hz), 131.5, 130.1, 126.6, 123.7, 68.4 (dd, *J* = 29.4, 19.6 Hz), 21.7. The diastereomeric ratio and the enantiomeric excess of the product were determined by chiral HPLC using a Chiracel IC column (*n*-hexane/*i*-PrOH = 80/20, flow rate: 0.5 mL/min, λ = 207 nm, τ = 20.6 min ; 23.6 min ; 49.1 min and 59.5 min.). IR (cm^{-1}) 3056, 1699, 1585, 1420, 1280, 1140, 1065, 810, 700, 515. HRMS (ESI) calcd for $C_{14}H_{11}F_2NaNO_2S$: 318.0371, found: 318.0360.

(*S*)-2,2-Difluoro-1-(4-anisyl)-2-((*S*)-*p*-tolylsulfinyl)ethan-1-ol (S_S,*S*)-**21a-16**

The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 50/50). 29% yield. 93:7 d.r., 98% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.60 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.37 (d, *J* = 22.6 Hz, 1H), 3.79 (s, 2H), 2.43 (s, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) –114,0 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 224.2 Hz, J_{BX} = $J_{H\text{-}F}$ = 22.3 Hz, $\Delta\nu_{AB}$ = 3035.4 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 160.30, 143.51, 132.32, 130.00, 129.58, 129.25, 126.79, 126.52, 113.90, 70.39 (dd, *J* = 28.9, 19.4 Hz), 55.39, 21.70. The diastereomeric ratio and the enantiomeric excess of the product were determined by chiral HPLC using a Chiracel IC column (*n*-hexane/*i*-PrOH = 80/20, flow rate: 0.5 mL/min, λ = 204 nm, τ = 13,0 min ; 15,5 min ; 31,7 min and 41,7 min.). IR (cm^{-1}) 3326, 1611, 1513, 1250, 1085, 1034, 975, 789, 522. HRMS (ESI) calcd for $C_{16}H_{16}F_2KO_3S$: 365.0420, found: 365.0432.

4.12. Removal of the chiral auxiliary

*4.12.1. Access to enantiopure α,α-difluoro-β-hydroxysulfone (S)-**24a-1***

(*S*)-2,2-Difluoro-1-phenyl-2-tosylethan-1-ol (*S*)-**24a-1**

To a solution of 2,2-difluoro-1-phenyl-2-(*p*-tolylsulfinyl) ethan-1-ol (S_S,*S*)-**21a-1** (1 equiv., 3.3 mg, 11.1 μmol) in 0.2 mL of anhydrous CH_2Cl_2 was added *m*-CPBA (78% of active oxygen, 1.5 equiv., 3.74 mg, 16.7 μmol) at 25 °C. The solution was stirred at this temperature for 24 hours. The reaction was quenched with a saturated solution of $Na_2S_2O_3$. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel using cyclohexane/AcOEt (100/0 to 80/20). Quantitative yield. 94% e.e. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.88 (d, *J* = 8.3 Hz, 2H), 7.51-7.45 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.40-7.36 (m, 3H), 5.56 (dd, *J* = 21.3 Hz, 2.1 Hz, 1H), 3.44-3.17 (br s, 1H), 2.48 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –111.9 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 237.1 Hz, J_{BX} = $J_{H\text{-}F}$ = 21.1 Hz, $\Delta\nu_{AB}$ = 5850 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 147.4, 133.8, 130.9, 130.3, 129.7, 129.7, 128.7, 128.3, 120.2 (dd, *J* = 288.8 Hz, 298.4 Hz), 71.5 (dd, *J* = 20.0 Hz, 26.3 Hz), 22.1. The enantiomeric excess of the product was determined by chiral HPLC using a Chiracel IC column (*n*-hexane/*i*-PrOH = 80/20, flow rate: 0.5 mL/min, λ = 220 nm, τ = 17.8 min and 20.1 min). See our previous paper.[8]

4.12.2. Access to a highly enantioenriched α,α-difluoromethyl alcohol by desulfonylation

(*S*)-2,2-Difluoro-1-phenylethan-1-ol (*S*)-**25-1**

Magnesium turnings (30 equiv., 68.26 mg, 2.59 mmol) were previously placed under vacuum. 0.3 mL of methanol and a minimal amount of iodine were added to the medium. The mixture was cooled to 0 ºC. A solution of (*S*)-2,2-difluoro-1-phenyl-2-tosylethan-1-ol (*S*)-**24a-1** (1 equiv., 27 mg, 0.086 mmol) in 0.7 mL of methanol was added. The reaction mixture was allowed to warm to 20 °C and stirred at this temperature for 16 h. The reaction was quenched with a saturated solution of ammonium chloride. The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 70/30). 66% yield. 95% e.e. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46-7.35 (m, 5H), 5.77 (td, *J* = 4.8 Hz, 55.9 Hz, 1H), 4.84 (td, *J* = 4.6 Hz, 10.1 Hz, 1H), 2.43 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –127.2 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 284.1 Hz, J_{AX} = $J_{H\text{-}F}$ = 55.9 Hz, J_{BX} = $J_{H\text{-}F}$ = 9.5 Hz, $\Delta\nu_{AB}$ = 278.5 Hz, 1F) and –128.0 (ABX system, J_{AB} = $J_{F\text{-}F}$ = 284.1 Hz, J_{AX} = $J_{H\text{-}F}$ = 55.9 Hz, J_{BX} = $J_{H\text{-}F}$ = 10.9 Hz, $\Delta\nu_{AB}$ = 278.8 Hz, 1F). The enantiomeric excess of the product was determined by chiral HPLC using a Chiracel IC column (*n*-hexane/*i*-PrOH = 95/5, flow rate: 0.5 mL/min, λ = 207

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nm, τ = 10.7 min and 11.7 min). These data are consistent with those already reported in the literature.[5a]

4.12.3. Access to highly enantioenriched α,α-difluoromethyl alcohols by desulfinylation with Mg(0) or PMHS/t-BuOK

(*S*)-2,2-Difluoro-1-phenylethan-1-ol (*S*)-**25-1** by PMHS/*t*-BuOK-mediated desulfinylation

To a stirred solution of 2,2-difluoro-1-phenyl-2-(*p*-tolyl sulfinyl)ethan-1-ol (S_S,*S*)-**21a-1** (1 equiv., 50 mg, 169 µmol) and *t*-BuOK (3 equiv., 56.8 mg, 506 µmol) in freshly distilled THF was added dropwise PMHS (3 equiv., 137 µL, 506 µmol). The mixture was stirred at 20 °C for 48 h in a sealed tube, then quenched with a solution of KOH in a H_2O/methanol (1:1, V/V) mixture and left under stirring for 2 h. The aqueous phase was extracted three times with Et_2O. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and with a saturated solution of NaCl, dried over anhydrous sodium sulfate, filtered over Celite® and activated charcoal and concentrated under reduced pressure. The crude was purified by chromatography on silica gel with cyclohexane/AcOEt (100/0 to 70/30). 52% yield. 88% e.e.

(*S*)-2,2-Difluoro-1-(4-anisyl)-ethan-1-ol (*S*)-**25-16** by Mg(0)-mediated desulfinylation

The same procedure as for the desulfonylation of (*S*)-**24a-1** was used on (S_S,*S*)-**21a-16**. The crude product was purified by chromatography on silica gel using with cyclohexane/AcOEt (100/0 to 60/40) as eluent. 64% yield. 86% e.e. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.34 (d, *J*= 8.7 Hz, 2H), 6.93 (d, *J*= 8.7 Hz, 2H), 5.74 (td, *J* = 5.1 Hz, 56.3 Hz, 1H), 4.77 (td, *J* = 4.7 Hz, 10.3 Hz, 1H), 3.81 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) –127.5 (app. dd, *J* = 56.2, *J* = 9.5 Hz, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 160.3, 131.8, 130.0, 129.7, 129.6, 128.6, 117.9, 116.0, 114.3, 114.0, 113.9, 73.4 (d, *J* =26 Hz), 55.5, 29.8. IR (cm^{-1}) 3414, 2924, 1515, 1250, 1068, 832, 552. HRMS (ESI) calcd for $C_9H_9F_2O_2$: 187.0576, found: 187.0591. [α_{589}] = +13.40 (20 °C, 0.7 g/100 mL, $CHCl_3$). The enantiomeric excess of the product was determined by chiral HPLC using a Chiracel IC column (*n*-hexane/*i*-PrOH = 98/2, flow rate: 0.5 mL/min, λ = 224 nm, τ = 27.2 min and 30.7 min).

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Appendix A. Supplementary data

Experimental details are provided in the Supporting Information.

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