Stereoselectivity of the Honda-Reformatsky reaction in reactions with ethyl bromodifluoroacetate with α-oxygenated sulfinylimines

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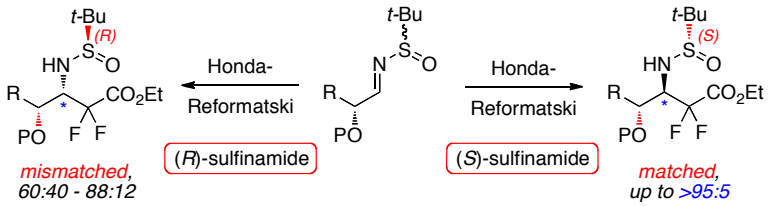


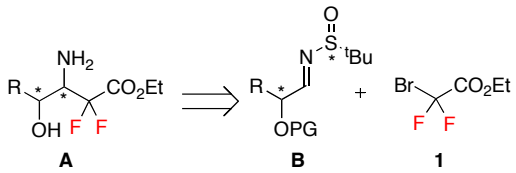
Abstract—The Reformatsky reaction of ethyl bromodifluoroacetate to α-oxygenated sulfinylimines is described. Using Honda-Reformatsky conditions, the reaction proceeds with double diastereodifferentiation, with the configuration of the sulfinyl group determining the stereochemical course of the reaction. Excellent diastereoselectivities (>94:6) are obtained for the matched cases. In contrast, reaction with sulfinylimines derived from unsubstituted alkanals proceeded with virtually no diastereoselectivity.

The introduction of fluorine in molecules of interest to modulate their properties is a major strategy in many application areas.[1,2,3] These include the pharmaceutical and agrochemical industries – around 20% of the commercially available pharmaceuticals and 30% of agrochemicals are fluorinated,[4] and performance materials, such as liquid crystals.[5] Given the abundance of amine containing bioactive compounds, their fluorination has received great attention.[6,7,8,9] The β-position of amino groups is often considered for fluorination given the resulting effect on their p$K_{a(H)}$ value and lipophilicity.[10,11] Fluorination will also have an impact on the amine hydrogen bonding properties, and will induce potentially strong conformational effects.[12]

The conformational properties and biological activities of β-amino acids have received great attention, including the corresponding α,α-difluoro-β-amino acids.[13,14,15,16] Their synthesis using direct C–C bond formations with fluorinated building blocks usually involve Reformatsky reaction of $BrCF_2COOEt$ **1** to imine derivatives (or their equivalents).[13] The synthesis of enantioenriched α,α-difluoro-β-amino acid derivatives using the Reformatsky reaction has been reported with imines derived from chiral amines, such as the *t*-butyl- and *p*-toluenesulfinylimines[7,17,18,19,20,21] and imines derived from (*R*)-phenyl glycinol.[13,22,23,24,25,26] Excellent diastereoselectivities are obtained with imines derived from aromatic aldehydes, while imines derived from aliphatic substrates generally give lower selectivities.

The β-amino alcohol moiety is a well-known pharmacophore in bioactive compounds, and the corresponding γ,γ-difluoro-β-aminoalcohols are thus of interest. Whereas nucleophilic addition to sulfinylimines that contain an α-oxygenated chiral centre is a popular method for the diastereoselective synthesis of β-amino alcohols,[19] we are not aware of examples of Reformatsky reactions (either with **1** or with $BrCH_2COOEt$) on these types of sulfinylimines. Only a few examples were found where **1** was reacted with imines derived from achiral amines and α-oxygenated aldehydes: the benzyl imine derived from glyceraldehyde acetonide was reported to react with a ~4:1 *syn*-selectivity,[27,28] while a complex C-glycosyl derived imine gave complete *syn*-selectivity.[29]

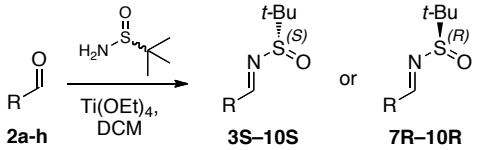
Scheme 1. Retrosynthetic analysis featuring a Reformatsky reaction.



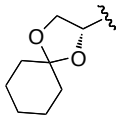
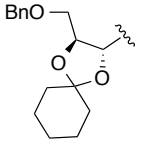
We were interested in investigating a short synthesis of the motif **A** (Scheme 1), a versatile intermediate for the synthesis of complex α,α-difluoro-β-amino acids and of 2,2-difluoro-3-amino carbohydrate analogues, via a Reformatsky reaction as shown in Scheme 1. The sulfinylimine auxiliaries were selected, given they are accessible in both enantiomeric forms, and because of the absence of concomitant β-lactam formation upon addition reaction. Addition reactions to substrates **B** using various organometallic derivatives have been described to occur with various levels of double diastereoselection, in which the chirality of the auxiliary is usually dominant.[20] Furthermore, Ellman has recently described the addition of a benzyl zinc reagent to either diastereomer of the *t*-butanesulfinyl imine derived from (*R*)-glyceraldehyde acetonide, which for the matched case proceeded with virtually complete stereoselectivity.[30] Herein we describe a study of the Reformatsky reaction using **1** with α-oxygenated sulfinylimines **B**, in which the anticipated double diastereoselection was investigated by combining both enantiomeric sulfinylimine auxiliaries with all chiral aldehydes employed.

The imines were synthesized from the corresponding aldehydes in good yields mainly using the $Ti(OEt)_4$ procedure.[31,32] As expected,[33] no epimerization of the α-stereocentre was observed with chiral aldehydes. Imines **3**–**6** were synthesized as model compounds to enable comparison with the stereoinduction exerted by the chiral auxiliaries without the additional bias of an α-oxygenated substituent.

Table 1. Synthesis of the *t*-butanesulfinylimines.



2a-h **3S–10S** **7R–10R**

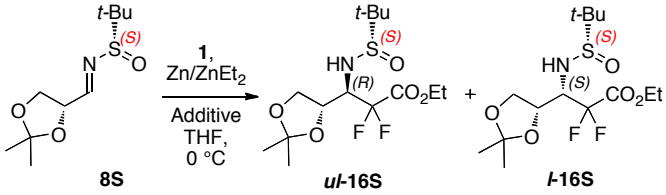
entry	R	Product	yield[a] (%)
1	Et	**3S**	72
2	$C_{11}H_{23}$	**4S**	87
3		**5S**	88
4		**6S**	79
5[b]		**7S**	82
6[b]		**7R**	71
7		**8S**	80
8		**8R**	86
9		**9S**	89
10		**9R**	88
11[b]		**10S**	83
12[b]		**10R**	85

[a] Isolated yield. [b] Enantiomers were synthesized. See Supporting Information

The Reformatsky reaction was first investigated by a short optimization effort using sulfiminine **8S**, which was predicted to proceed with matched double diastereoselection.[30] Promotion by indium[34] (entry 1) gave no reaction, even at 60 °C. The use of zinc was successful, and the desired product was obtained in 46% yield and a 72:28 diastereoisomeric ratio (dr) (entry 2). Modification of the stoichiometry afforded an improved 61% yield and 85:15 dr (entry 3). The use of activated zinc (dil HCl), and DCM as co-solvent enhanced the yield, but proceeded with slightly lower dr (entry 4). The use of Et_2O or toluene as co-solvent gave similar results (not shown). Zn activation by DMSO/TMSCl[35] failed to induce reaction (entry 5). Pleasingly, using Et_2Zn under Honda-Reformatsky conditions, which employs

the Wilkinson catalyst to promote Zn insertion,[36,37] a single diastereoisomer was obtained in 45% yield (entry 6), which could be increased to 61% upon doubling the amount of **1** (entry 7). Replacement of the Wilkinson catalyst by $NiCl_2(PPh_3)_2$ (entry 8)[38] or of Et_2Zn by Me_2Zn (entry 9) was not possible.

Table 2. Optimisation of the Reaction.[a]

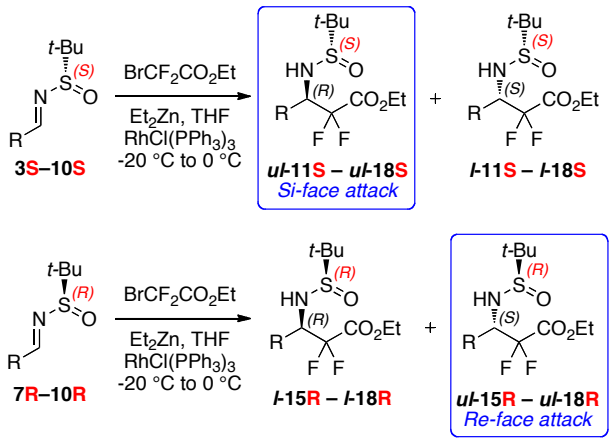


entry	**1** (equiv)	metal (equiv)	additive (equiv)	d.r[b]	yields (%)[c]
1	2	In (2)	-	-	NR
2	4	Zn (3)	-	72:28	46
3	5	Zn (4)	-	85:15	61
4	5	Zn[d] (4)	-[e]	75:25	78
5	5	Zn[f] (4)	-	-	<5
6	1.5	Et_2Zn (1.5)	$RhCl(PPh_3)_3$ (3)	>95:5	45
7	3	Et_2Zn (2)	$RhCl(PPh_3)_3$ (3)	>95:5	61
8	1.5	Et_2Zn (1.5)	$NiCl_2(PPh_3)_2$ (5)	-	NR
9	1.1	Me_2Zn (3)	$RhCl(PPh_3)_3$ (3)	-	NR

[a] The prefix *l* (like) indicates that the sulfinyl group and the newly formed amine stereocentre have the same absolute configuration (and otherwise for *ul* (unlike)). The suffix R or S in the numbering refers to the absolute configuration of the sulfinylimine auxiliary. [b]Determined by ^{19}F NMR (crude reaction mixture) [c] Isolated yield. [d] dil aq. HCl activation. [e] DCM was used as co-solvent. [f] DMSO/TMSCl activation.

Next, the Reformatsky reaction was investigated on a range of sulfinylimines (Table 3).

Table 3. Scope of the Reaction.[a]



entry	R	imine	major product	yield[b] (%)	d.r. (*ul*:*l*)
1	Et	**3S**	***ul*-11S**	64	53:47
2	$C_{11}H_{23}$	**4S**	***ul*-12S**	58	53:47
3	BnO	**5S**	***ul*-13S**	46	88:12
4	BnO	**6S**	-	NR	-
5[c]	BnO	**7S**	***ul*-15S**	57	94:6
6[c]		**7R**	***ul*-15R**	46	54:46
7	O O	**8S**	***ul*-16S**	62	>95:5
8		**8R**	***ul*-16R**	59	88:12
9	O O	**9S**	***ul*-17S**	52	>95:5
10		**9R**	***ul*-17R**	56	81:19
11[c]	BnO O O	**10S**	***ul*-18S**	62 (67)	>95:5
12[c]		**10R**	***ul*-18R**	48	60:40

[a] see Footnote a, Table 2. [b] Isolated yield. [c] Enantiomers were synthesized. Shown as is to facilitate stereochemical analysis.

Reaction with the aliphatic sulfinylimines **3S** and **4S** was not diastereoselective under the Honda-Reformaksky conditions (entries 1,2). We also observed slight variations in diastereoselectivity

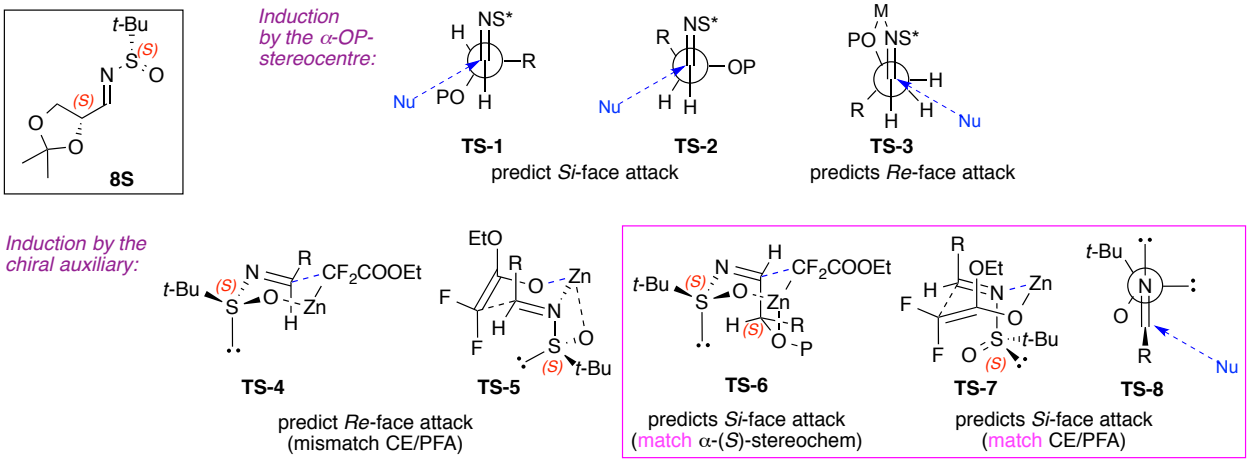
depending on the age of the Et_2Zn and rate of its addition (53:47 to 60:40), but always with the same major diastereomer. The low dr was surprising, given the much higher values obtained by Staas[18] and Soloshonok (up to 86:14 even in refluxing THF, using Zn)[17] for similar sulfinylimines derived from linear aliphatic aldehydes. However, Reformatsky reaction of **5S**, which has an α-benzyloxy substituent, proceeded with much increased diastereoselectivity (entry 3). Interestingly, the sterically hindered substrate **6S** was unreactive under the conditions used (entry 4). Pleasingly, the Reformatsky reaction of substrate **7S** (entry 5), derived from (*S*)-lactaldehyde and the (*S*)-configured chiral auxiliary, proceeded with enhanced diastereoselectivity compared to the benzyloxymethyl-derived sulfinylimine **5S**. In contrast, when the enantiomeric chiral auxiliary was used (**7R**, entry 6), the diastereoselectivity was much reduced, evidencing a double diastereodifferentiation effect. This was also observed for the other chiral aldehydes derived from glyceraldehyde and threose, for which the matched cases proceeded with excellent diastereoselectivity (entries 7,9,11).

The relative configuration of the major diastereomers obtained from reaction of the aliphatic-derived **3S**, and the α-alkoxy-derived **8S** and **8R** could be determined by X-ray crystallographic analysis (See Supporting Information). In all cases the *ul*-relative configuration was confirmed. Both products ***ul*-16S** and ***ul*-16R** are derived from the same glyceraldehyde enantiomer but with differently configured chiral auxiliaries, and the different configuration of the formed amine stereocentre clearly proved that the diastereoselection was determined by the configuration of the auxiliary, and not by the α-stereocentre. On that basis, the stereochemistry of the other major and minor isomers was assigned.

The relative stereochemistry determined for ***ul*-11S** was most unexpected, given the precedence of both Staas and Soloshonok, who reported the other diastereomer as the major product of the Reformatsky reaction on alkyl-derived sulfinylimines. However, these Reformatsky reactions were performed under different conditions (Zn, THF, reflux or room temperature, versus $ZnEt_2/RhCl(PPh_3)_3$, THF, 0 °C in our case), and it should be remembered that the dr in our case was very low. On the other hand, our results correspond to the stereoinduction determined previously by Ellman for reactions of

sulfinylimines derived both from aliphatic aldehydes, and from (*S*)-glyceraldehyde acetonide, with benzyl zinc reagents, including the matched/mismatched stereoinduction.[30] Their benzyl zinc reagent was synthesized from the corresponding benzyl chloride using $ZnCl_2$/Mg/LiCl (Knochel conditions[39]).

Figure 1. Models to explain the stereoinduction/double diastereodifferentiation.



The stereoinduction by the α-oxygenated chiral centre for **8S** can be deduced from the Cornforth-Evans/polar Felkin-Anh models **TS-1** and **TS-2** (Figure 2),[40] which both predict the observed *Si*-face attack. In contrast, the cyclic "Cram model" **TS-3**,[41] involving coordination of the imine nitrogen and the α-alkoxy group, predicts *Re* face attack.

Several models have been proposed to rationalize the induction by the sulfinylimine auxiliary.[20] The cyclic Ellman transition state **TS-4** has been suggested for the Reformatsky reaction (Zn, refluxing THF) of **1** to sulfinylimines derived from aromatic and aliphatic aldehydes,[17] and which successfully explains the Staas and Soloshonok results[17,18] (as well as for Reformatsky reactions using $BrCH_2COOEt$)[42,43]. However, given it predicts *Re* face attack (for an (*S*)-configured sulfinylimine), it is not consistent with our findings. Equally, **TS-5**,[44,45] involving a Zn-enolate, predicts the wrong facial selectivity. However, this model correctly explained the facial selectivity of addition with allyl zinc to an aryl sulfinylimine (in THF).[43] In contrast, the Barrow chelation model **TS-6**,[46] involving chelation

with both the S=O and the α-alkoxy groups and a rapid sulfinyl imine *E*/*Z* isomerization, predicts the correct stereochemical outcome, including the double diastereodifferentiation (though now due to the avoidance of a sterically unfavourable interaction with the sulfinyl group as opposed to involvement of **TS-1**/**TS-2**). The transition state **TS-7** proposed by Marek, also for reaction with allyl zinc derivatives in THF, correctly predicts *Si*-face attack as well.[47] This model differs from **TS-5** in that chelation is only involving the imine nitrogen atom, with the S=O dipole oriented antiperiplanar to the imine lone pair. Both **TS-7** and **TS-5** (which predict opposing facial selectivity) have been successfully used to explain the outcome of additions of allyl zinc to sulfinylimines,[43,47] which shows that the exact conditions, especially the amount of coordinating species in solution, can influence the facial selectivity. However, for a Reformatsky reaction the additional *pseudo*-axial OEt-substituent could disfavor **TS-7**. Finally, an open transition state **TS-8** proposed by Davis[48] also predict the observed *Si*-facial attack. This model was used by Ellman to explain the stereochemical outcome of the aforementioned addition of benzyl zinc reagents to both aryl- and (*S*)-glyceraldehyde-derived sulfinylimines (involving excess of coordinating ions and a coordinating solvent).[30]

The much-increased selectivities for substrates **5**,**7**–**10** compared to **3**,**4** suggest a chelation role of the α-oxygen containing substituent, which points to the Barrow transition state **TS-6**. For the alkyl sulfinylimines **3**,**4**, it is unlikely that the required *E*/*Z* isomerisation is occurring/complete, given there is no chelating α-substituent to drive this process.

Conclusions

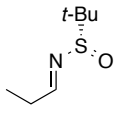
The Reformatsky reaction involving ethyl bromodifluoroacetate was investigated both with sulfinylimines derived from aldehydes with a chiral α-oxygenated substituent, as well as derived from aliphatic aldehydes. Reformatsky reaction of the former proceeds with double diastereodifferentiation, with the configuration of the chiral auxiliary determining the stereoinduction. The stereochemical outcome is consistent with the Barrow model.

Experimental Section

General procedure for the synthesis of *t*-butanesulfinylimines (Table 1).[30]

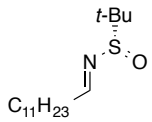
To a mixture of aldehyde (1 equiv) and sulfinamide (1.05 equiv) in CH_2Cl_2 was added $Ti(OEt)_4$ (3-5 equiv). After stirring at rt overnight, water was added. Stirring for a further 15 min was followed by filtration over a pad of $MgSO_4$ and Celite®. The filter cake was washed with EtOAc and the filtrate concentrated under reduced pressure. The residue was purified via filtration over a pad of silica to afford pure sulfinylimine (pale-yellow oils).

(S_S,E)-*N*-(propylidene)-2-methyl-2-propanesulfinamide (**3S**)[49]



Propionaldehyde (0.100 g, 1.72 mmol), (*S*)−2−methyl−2−propanesulfinamide (0.219 g, 1.81 mmol) and $Ti(OEt)_4$ (1.18 g, 5.17 mmol) yielded **3S** (0.201 g, 1.25 mmol, 72%) as a pale yellow oil. R_f 0.27 (hexane/EtOAc 75:25). $[\alpha]_D$ +338.4 (c 0.12, $CHCl_3$, 26 °C), lit. (***ent*-3S**) $[\alpha]_D$ –328.5 (c 1.0, $CHCl_3$, 23 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (t, $^3J_{HH}$=4.3 Hz, 1H), 2.55 (dq, $^3J_{HH}$=7.4 Hz, $^3J_{HH}$=4.3 Hz, 2H), 1.20 (s, 9H), 1.20 (t, $^3J_{HH}$=7.4 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 56.5, 29.5, 22.3 (3C), 9.6 ppm. NMR spectra correspond to the reported data for ***ent*-3S**.[49]

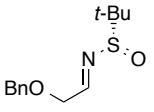
(S_S,E*)-N*-[dodecylidene]-2-methyl-2-propanesulfinamide (**4S**)



Dodecanal (0.30 mL, 0.249 g, 1.34 mmol), (*S*)−2−methyl−2−propanesulfinamide (0.170 g, 1.41 mmol) and $Ti(OEt)_4$ (1.53 g, 6.70 mmol) yielded **4S** (0.366 g, 1.17 mmol, 87%) as a pale yellow oil. R_f 0.47 (hexane/EtOAc 75:25). $[\alpha]_D$ +166.0 (c 0.21, $CHCl_3$, 28 °C). IR (neat) 2923 (s), 2854 (m), 1622 (m), 1457 (w), 1363 (w), 1087 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (t, $^3J_{HH}$=4.7 Hz, 1H), 2.52 (dt, $^3J_{HH}$=7.4 Hz, $^3J_{HH}$=4.7 Hz, 2H), 1.70–1.60 (m, 2H), 1.51–1.24 (m, 16H), 1.20 (s, 9H), 0.89 (t, $^3J_{HH}$=7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 56.5, 36.1, 31.9, 29.6 (2C), 29.5, 29.3

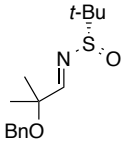
(2C), 29.2, 25.5, 22.7, 22.3 (3C), 14.1 ppm. HRMS (MS+) for $C_{16}H_{34}NOS$ $(M+H)^+$ calcd 288.2356, found 288.2356.

(S_S,E)-*N*-[2-Benzyloxyethylidene]-2-methyl-2-propanesulfinamide (**5S**)



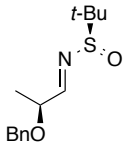
To benzyloxyacetaldehyde[50] (0.250 g, 1.67 mmol) in CH_2Cl_2 (3.5 mL) were added (*S*)−2−methyl−2−propanesulfinamide (0.212 g, 1.75 mmol) and $CuSO_4$ (0.558 g, 3.50 mmol). The resultant mixture was stirred at rt for 15 h then filtered over Celite® to afford the desired crude product. Purification over a short pad of silica eluting with PE/EtOAc 75:25 yielded **5S** (0.371 g, 1.46 mmol, 88%) as a pale yellow oil. R_f 0.21 (hexane/ethyl acetate 70:30). $[\alpha]_D$ +161.6 (c 0.09, $CHCl_3$, 26 °C), lit. (***ent*-5S**)[51] $[\alpha]_D$ –212 (c 1.0, $CHCl_3$, 23 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (t, $^3J_{HH}$ 3.2 Hz, 1H), 7.40–7.29 (m, 5H), 4.65 (s, 2H), 4.45 (dd, $^2J_{HH}$=16.3, $^3J_{HH}$=3.2 Hz, 1H), 4.39 (dd, $^2J_{HH}$=16.3, $^3J_{HH}$=3.2 Hz, 1H), 1.23 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 137.2, 128.5, 128.0, 127.9, 73.3, 71.3, 57.0, 22.4 ppm. NMR spectra correspond to the reported data for ***ent*-5S**.[51]

(S_S,E)-*N*-[2-(Benzyloxy)-2-methylpropylidene]-2-methyl-2-propanesulfinamide (**6S**)



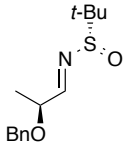
2–Benzyloxy–2–methylpropanal[52] (0.120 g, 0.673 mmol), (*S*)−2−methyl−2−propanesulfinamide (0.086 g, 0.707 mmol) and $Ti(OEt)_4$ (0.768 g, 3.37 mmol) yielded **6S** (0.149 g, 0.529 mmol, 79%) as a pale yellow oil. R_f 0.47 (PE/Et_2O 60:40). $[\alpha]_D$ +210.6 (c 0.50, $CHCl_3$, 22 °C). IR (neat) 2979 (w), 1622 (w), 1160 (m), 1087 (s), 1059 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.40–7.23 (m, 5H), 4.48 (d, $^2J_{HH}$=11.1 Hz, 1H), 4.45 (d, $^2J_{HH}$=11.1 Hz, 1H), 1.50 (s, 3H), 1.48 (s, 3H), 1.23 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 138.4, 128.4, 127.5, 127.6, 78.1, 66.4, 56.9, 24.4, 24.0, 22.5 ppm, HRMS (MS+) for $C_{15}H_{23}NNaO_2S$ $(M+Na)^+$ calcd 304.1342, found 304.1338.

(R_S,E)-*N*-[(2*S*)-2-(Benzyloxy)propylidene]-2-methyl-2-propanesulfinamide (***ent*-7S**)[33]



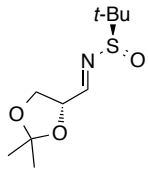
(2*S*)–2–Benzyloxypropanal[52] (0.150 g, 0.914 mmol), (*R*)–2–methyl–2–propanesulfinamide (0.122 g, 1.01 mmol) and $Ti(OEt)_4$ (0.625 g, 2.74 mmol) yielded ***ent*-7S** (0.200 g, 0.748 mmol, 82%) as a pale yellow oil. R_f 0.60 (hexane/EtOAc 50:50). $[\alpha]_D$ –222 (c 0.52, EtOH, 22 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, $^3J_{HH}$=4.6 Hz, 1H), 7.41–7.23 (m, 5H), 4.66 (d, $^2J_{HH}$=11.7 Hz, 1H), 4.54 (d, $^2J_{HH}$=11.7 Hz, 1H), 4.35 (dq, $^3J_{HH}$=6.7 Hz, $^3J_{HH}$=4.6 Hz, 1H), 1.41 (d, $^3J_{HH}$=6.7 Hz, 3H), 1.22 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 137.6, 128.5, 127.9, 127.8, 76.3, 71.6, 56.9, 22.4, 18.7 ppm. NMR spectra correspond to the reported data.[33]

(S_S,E)-*N*-[(2*S*)-2-(Benzyloxy)propylidene]-2-methyl-2-propanesulfinamide (***ent*-7R**)



(2*S*)–2–Benzyloxypropanal[52] (0.150 g, 0.914 mmol), (*S*)–2–methyl–2–propanesulfinamide (0.116 g, 0.959 mmol) and $Ti(OEt)_4$ (0.833 g, 3.65 mmol) yielded ***ent*-7R** (0.173 g, 0.647 mmol, 71%) as a pale yellow oil. R_f 0.40 (hexane/EtOAc 50:50). $[\alpha]_D$ +67.3 (c 0.53, EtOH, 22 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, $^3J_{HH}$=4.5 Hz, 1H), 7.43–7.28 (m, 5H), 4.67 (d, $^2J_{HH}$=11.6 Hz, 1H), 4.50 (d, $^2J_{HH}$=11.6 Hz, 1H), 4.34 (dq, $^3J_{HH}$=6.6 Hz, $^3J_{HH}$=4.5 Hz, 1H), 1.43 (d, $^3J_{HH}$=6.6 Hz, 3H), 1.24 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 137.7, 128.5, 127.9, 127.8, 76.2, 71.5, 56.8, 22.5, 18.5 ppm. NMR spectra correspond to the reported data.[33]

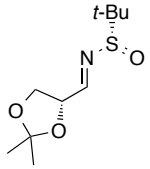
(R_S,E)-*N*-[(2*S*)-2,3-(isopropylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**8R**)



2,3–*O*,*O*–Isopropylidene–D–glyceraldehyde[53] (0.500 g, 3.84 mmol), (*R*)–2–methyl–2–propanesulfinamide (0.489 g, 4.03 mmol) and $Ti(OEt)_4$ (4.38 g, 19.2 mmol) yielded **8R** (0.771 g, 3.30 mmol, 86%) as a pale yellow oil. R_f 0.21 (hexane/EtOAc 70:30). $[\alpha]_D$ –198.6 (c 0.84, $CHCl_3$, 26 °C). IR (neat) 2984 (m), 2873 (m), 1626 (s), 1060 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, $^3J_{HH}$=4.5 Hz, 1H), 4.83 (ddd, $^3J_{HH}$=7.6 Hz, $^3J_{HH}$=5.5 Hz, $^3J_{HH}$=4.5 Hz, 1H), 4.25

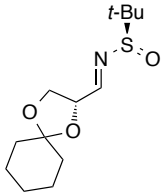
(dd, $^2J_{HH}$=8.7 Hz, $^3J_{HH}$=7.6 Hz, 1H), 4.00 (dd, $^2J_{HH}$=8.7 Hz, $^3J_{HH}$=5.5 Hz, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.20 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 111.0, 76.7, 67.1, 57.2, 26.4, 25.4, 22.3 ppm. HRMS (MS+) for $C_{10}H_{19}NNaO_3S$ $(M+Na)^+$ calcd 256.0983, found 256.0978. NMR spectra correspond to the reported data.[30]

(S_S,E)-*N*-[(2*S*)-2,3-(isopropylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**8S**)



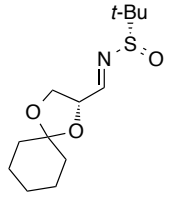
2,3–*O*,*O*–Isopropylidene–D–glyceraldehyde[53] (1.05 g, 8.07 mmol), (*S*)–2–methyl–2–propanesulfinamide (1.03 g, 8.47 mmol) and $Ti(OEt)_4$ (7.36 g, 32.3 mmol) yielded **8S** (1.50 g, 6.43 mmol, 80%) as a pale yellow oil. R_f 0.6 (PE/EtOAc 50:50). $[\alpha]_D$ +248 (c 0.49, EtOH, 23 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, $^3J_{HH}$=4.1 Hz, 1H), 4.85 (ddd, $^3J_{HH}$=6.8 Hz, $^3J_{HH}$=5.1 Hz, $^3J_{HH}$=4.1 Hz, 1H), 4.23 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=6.8 Hz, 1H), 4.05 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=5.1 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.21 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 110.8, 76.9, 67.2, 57.0, 26.4, 25.4, 22.3 ppm. NMR spectra correspond to the reported data.[30]

(R_S,E)-*N*-[(2*S*)-2,3- cyclohexylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**9R**)



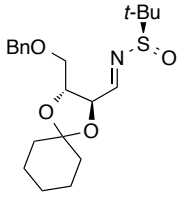
2,3–*O*,*O*–Cyclohexylidene–D–glyceraldehyde[54] (1.00 g, 5.88 mmol), (*R*)–2–methyl–2–propanesulfinamide (0.748 g, 6.17 mmol) and $Ti(OEt)_4$ (6.70 g, 29.4 mmol) yielded **9R** (1.41 g, 5.16 mmol, 88%) as a pale yellow oil. R_f 0.29 (hexane/EtOAc 70:30). $[\alpha]_D$ – 216.6 (c 0.49, $CHCl_3$, 20 °C). IR (neat) 2934 (m), 2863 (m), 1625 (s), 1084 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, $^3J_{HH}$=4.5 Hz, 1H), 4.83 (ddd, $^3J_{HH}$=7.2 Hz, $^3J_{HH}$=5.5 Hz, $^3J_{HH}$=4.5 Hz, 1H), 4.24 (dd, $^2J_{HH}$=8.6 Hz, $^3J_{HH}$=7.2 Hz, 1H), 4.01 (dd, $^2J_{HH}$=8.6 Hz, $^3J_{HH}$=5.5 Hz, 1H), 1.77–1.53 (m, 8H), 1.48–1.34 (m, 2H), 1.21 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 111.6, 76.5, 66.8, 57.2, 36.0, 35.0, 25.0, 23.83, 23.80, 22.4 ppm. HRMS (MS+) for $C_{13}H_{23}NNaO_3S$ $(M+Na)^+$ calcd 296.1291, found 296.1296.

(S_S,E)-*N*-[(2*S*)-2,3- Cyclohexylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**9S**)



2,3–*O*,*O*–Cyclohexylidene–D–glyceraldehyde[54] (1.0 g, 5.88 mmol), (*S*)–2–methyl–2–propanesulfinamide (0.748 g, 6.17 mmol) and $Ti(OEt)_4$ (6.70 g, 29.4 mmol) yielded **9S** (1.43 g, 5.23 mmol, 89%) as a pale yellow oil. R_f 0.53 (PE/EtOAc 60:40). $[\alpha]_D$ +193 (c 0.53, EtOH, 22 °C). IR (neat) 2934 (m), 2359 (s), 1625 (m), 1364 (m), 1088 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, $^3J_{HH}$=4.2 Hz, 1H), 4.84 (ddd, $^3J_{HH}$=6.7 Hz, $^3J_{HH}$=5.1 Hz, $^3J_{HH}$=4.2 Hz, 1H), 4.22 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=6.7 Hz, 1H), 4.04 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=5.1 Hz, 1H), 1.73–1.54 (m, 8H), 1.48–1.37 (m, 2H), 1.20 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 111.5, 76.7, 67.0, 57.1, 36.1, 35.0, 25.0, 23.9, 23.9, 22.4 ppm. MS (ESI+) (*m*/*z*) 274 $(M+H)^+$. HRMS (MS+) for $C_{13}H_{23}NNaO_3S$ $(M+Na)^+$ calcd 296.1291, found 296.1297.

(R_S,E)-*N*-[(2*R*,3*R*)-4-(Benzyloxy)-2,3-(cyclohexylidenedioxy)butylidene]-2-methyl-2-propanesulfinamide (***ent*-10S**)

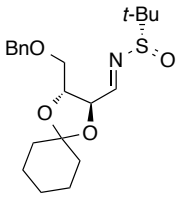


SO_3•pyridine (3.27 g, 20.5 mmol, 3.0 equiv), Et_3N (3.34 mL, 23.9 mmol, 3.5 equiv), DMSO (8 mL) and CH_2Cl_2 (17 mL) were combined and stirred at –20 °C for 0.5 h. The corresponding alcohol ($[\alpha]_D$ –4.02 (c 1.3, $CHCl_3$, 21 °C), lit. +0.90 (c 1.3, $CHCl_3$, 24 °C, enantiomer)[55](2.00 g, 6.84 mmol, 1 equiv), DMSO (8 mL) and DCM were stirred at –20 °C in a separate flask and to this solution was added dropwise via cannula the solution of SO_3. The resultant mixture was allowed to stir below –10 °C for 1 h then at rt for 3 h. Quenching with saturated aqueous NH_4Cl solution and extraction with EtOAc (2 × 15 mL) and Et_2O (2 × 15 mL) was followed by drying over $MgSO_4$ and concentrating *in vacuo* to afford bright yellow oil. Column chromatography (PE/EtOAc 75:25 to 70:30) afforded 1.63 g (5.61 mmol, 82%) of the pure aldehyde **2h** as a colourless oil. R_f 0.31 (PE/EtOAc 75:25). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (d, $^3J_{HH}$=1.6 Hz, 1H), 7.40–7.28 (m, 5H), 4.62 (s, 2H), 4.32–

4.22 (m, 2H), 3.67 (dd, $^3J_{HH}$=4.5 Hz, $^3J_{HH}$=1.1 Hz, 2H), 1.75–1.54 (m, 8H), 1.49–1.34 (m, 2H) ppm. The aldehyde was used immediately after purification.

4–*O*–Benzyl–2,3–*O*,*O*–cyclohexylidene–D–threose **2h** obtained as described above (800 mg, 2.76 mmol), (*R*)–2–methyl–2–propanesulfinamide (367 mg, 3.03 mmol) and $Ti(OEt)_4$ (3.14 g, 13.8 mmol) yielded ***ent*-10S** (900 mg, 2.29 mmol, 83%) as a pale yellow oil. R_f 0.7 (PE/EtOAc 50:50). $[\alpha]_D$ –104 (c 0.67, EtOH, 23 °C). IR (neat) 2933 (m), 2861 (m), 2359 (m), 2342 (m), 1084 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, $^3J_{HH}$=4.7 Hz, 1H), 7.39–7.28 (m, 5H), 4.67–4.55 (m, 3H), 4.22 (ddd, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=5.6 Hz, $^3J_{HH}$=4.4 Hz, 1H), 3.68 (dd, $^2J_{HH}$=10.4 Hz, $^3J_{HH}$=4.4 Hz, 1H), 3.64 (dd, $^2J_{HH}$=10.4 Hz, $^3J_{HH}$=5.6 Hz, 1H), 1.74–1.57 (m, 8H), 1.52–1.31 (m, 2H), 1.14 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 137.7, 128.4 (2C), 127.8 (3C), 112.0, 79.0, 77.9, 73.6, 69.8, 57.1, 36.5, 36.1, 25.0, 23.9, 23.7, 22.3 (3C) ppm. MS (ESI+) (*m/z*) 416 $(M+Na)^+$. HRMS (MS+) for $C_{21}H_{31}NNaO_4S$ $(M+Na)^+$ calcd 416.1866, found 416.1873.

(S_S,E)-*N*-[(2*R*,3*R*)-4-(benzyloxy)-2,3-(cyclohexylidenedioxy)butylidene]-2-methyl-2-propanesulfinamide (***ent*-10R**)



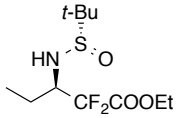
4–*O*–Benzyl–2,3–*O*,*O*–cyclohexylidene–D–threose **2h** obtained as described above (900 mg, 3.1 mmol), (*S*)–2–methyl–2–propanesulfinamide (394 mg, 3.26 mmol) and $Ti(OEt)_4$ (3.54 g, 15.5 mmol) yielded ***ent*-10R** (1.03 g, 2.63 mmol, 85%) as a pale yellow oil. R_f 0.7 (PE/EtOAc 50:50). $[\alpha]_D$ +156 (c 0.47, EtOH, 23 °C). IR (neat) 2934 (m), 2862 (m), 2359 (m), 2342 (m), 1087 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, $^3J_{HH}$=4.2 Hz, 1H), 7.39–7.28 (m, 5H), 4.67–4.59 (m, 3H), 4.28 (ddd, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=5.2 Hz, $^3J_{HH}$=4.2 Hz, 1H), 3.72 (dd, $^2J_{HH}$=10.6 Hz, $^3J_{HH}$=4.2 Hz, 1H), 3.68 (dd, $^2J_{HH}$=10.6 Hz, $^3J_{HH}$=5.2 Hz, 1H), 1.76–1.57 (m, 8H), 1.48–1.35 (m, 2H), 1.20 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 137.9, 128.4 (2C), 127.7 (3C), 111.9, 78.7, 77.8, 73.6, 69.7, 57.2, 36.5, 36.0, 25.0, 23.9, 23.7, 22.4 (3C) ppm. MS (ESI+) (*m/z)* 416 $(M+Na)^+$. HRMS (MS+) for $C_{21}H_{31}NNaO_4S$ $(M+Na)^+$ calcd 416.1866, found 416.1864.

General procedure for the Honda-Reformatski reaction (Table 3).

A mixture of sulfinylimine (1 equiv), $RhCl(PPh_3)_3$ (3 mol%) in THF (7.5 mL/mmol) was cooled to –20 °C. **1** (3 equiv) was added immediately followed by dropwise addition of Et_2Zn (1.0M in hexane, 2 equiv). The mixture was allowed to warm up to 0 °C over 30 min and stirring was continued for 1 h. Quenching with sat. NH_4Cl was followed by extraction with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography gave the products as pale-yellow oils unless mentioned otherwise.

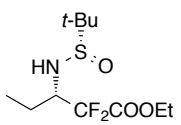
Reaction with sulfinylimine **3S** (100 mg, 0.620 mmol) yielded **11S** (53:47 *dr*). Chromatography (PE/EtOAc 70:30) afforded an inseparable mixture of diastereoisomers (114 mg, 0.400 mmol, 64%). Analytical samples of pure diastereoisomers were obtained by HPLC (hexane/EtOAc 70:30).

Major isomer: (3*R*,*S*s)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate ***ul*-11S** (pale yellow oil): R_f



0.20 (hexane/EtOAc 70:30). $[\alpha]_D$ +62.9 (c 0.19, $CHCl_3$, 21 °C). IR (in $CDCl_3$) 3207 (br), 2982 (m), 1773(s), 1062 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (dq, $^2J_{HH}$=10.7, $^3J_{HH}$=7.2 Hz, 1H), 4.29 (dq, $^2J_{HH}$=10.7, $^3J_{HH}$=7.1 Hz, 1H), 3.81–3.66 (m, 1H), 3.15 (d, $^3J_{HH}$=8.9 Hz, 1H), 1.98–1.86 (m, 1H), 1.65–1.52 (m, 1H), 1.36 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.20 (s, 9H), 1.14 (t, $^3J_{HH}$=7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{CF}$=32.3 Hz), 114.8 (t, $^1J_{CF}$=255.7 Hz), 62.8, 60.8 (dd, $^2J_{CF}$=25.7, 24.2 Hz), 56.5, 22.6, 22.4 (3C), 13.8, 10.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –110.4 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=7.5 Hz), –119.1 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=17.2 Hz) ppm. MS (ESI+) (*m*/*z*) 349 $(M+Na+MeCN)^+$. HRMS (MS+) for $C_{11}H_{21}F_2NNaO_3S$ $(M + Na)^+$ calcd 308.1102, found 308.1106.

Minor isomer: (3*S*,*S*s)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate ***l*-11S** (pale yellow oil): R_f

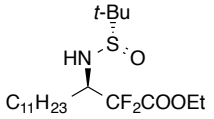


0.23 (hexane/EtOAc 70:30). $[\alpha]_D$ +26.6 (c 0.51, $CHCl_3$, 19 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (q, $^3J_{HH}$=7.1 Hz, 2H), 3.80–3.66 (m, 1H), 3.57 (d, $^3J_{HH}$=9.3 Hz, 1H),

1.91–1.78 (m, 1H), 1.66–1.52 (m, 1H), 1.38 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.24 (s, 9H), 1.06 (t, $^3J_{HH}$=7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{CF}$=31.9 Hz), 114.7 (t, $^1J_{CF}$=256.4 Hz), 63.3, 60.4 (dd, $^2J_{CF}$=25.3, 23.8 Hz), 56.9, 22.7 (3C), 22.3, 13.8, 10.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –109.9 (dd, $^2J_{FF}$=264.3, $^3J_{HF}$=7.5 Hz),–118.4 (dd, $^2J_{FF}$=264.3 Hz, $^3J_{HF}$=15.6 Hz) ppm. MS (ESI+) (*m/z*) 308 $(M+Na)^+$. HRMS (MS+) for $C_{11}H_{21}F_2NNaO_3S$ $(M + Na)^+$ calcd 308.1102, found 308.1106.

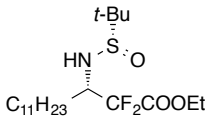
Reaction with sulfinylimine **4S** (150 mg, 0.522 mmol) yielded **12S** (53:47 *dr*). Chromatography (hexane/EtOAc 90:10→65:35) afforded an inseparable mixture of diastereoisomers (125 mg, 0.304 mmol, 58%). Analytical samples of pure diastereoisomers were obtained by HPLC (hexane/EtOAc 75:25).

Major isomer: (3*R*,S_s)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluorotetradecanoate ***ul*-12S** (pale yellow oil):



R_f 0.19 (hexane/EtOAc 75:25). $[\alpha]_D$ +43.9 (c 0.54, $CHCl_3$, 21 °C). IR (in $CDCl_3$) 3206 (br w), 2924 (s), 2854 (s), 1774 (s), 1057 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (dq, $^2J_{HH}$=10.9, $^3J_{HH}$=7.2 Hz, 1H), 4.29 (dq, $^2J_{HH}$=10.9, $^3J_{HH}$=7.2 Hz, 1H), 3.79 (ddddd app. as ddtd, $^3J_{HF}$=16.1, $^3J_{HH}$=8.8, $^3J_{HF}$=8.6, $^3J_{HH}$=8.6, $^3J_{HH}$=3.8 Hz, 1H), 3.10 (d, $^3J_{HH}$=8.8 Hz, 1H), 1.87–1.76 (m, 1H), 1.73–1.59 (m, 1H), 1.59–1.22 (m, 18H), 1.36 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.20 (s, 9H), 0.88 (t, $^3J_{HH}$=7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{CF}$=33.0 Hz), 114.9 (t, $^1J_{CF}$=255.4 Hz), 62.9, 59.4 (dd, $^2J_{CF}$=26.3 Hz, $^2J_{CF}$=23.4 Hz), 56.6, 31.9, 29.6 (4C), 29.3, 29.3 (2C), 25.2, 22.7, 22.5 (3C), 14.1, 13.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –110.8 (dd, $^2J_{FF}$=261.1 Hz, $^3J_{HF}$=8.6 Hz), –118.8 (dd, $^2J_{FF}$=261.1 Hz, $^3J_{HF}$=16.1 Hz) ppm. MS (ESI+) (*m/z*) 475 $(M+Na+MeCN)^+$. HRMS (MS+) for $C_{20}H_{39}F_2NNaO_3S$ $(M+Na)^+$ calcd 434.2511, found 434.2516.

Minor isomer: (3*S*,S_s)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluorotetradecanoate ***l*-12S** (pale yellow oil): R_f



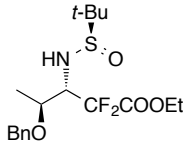
0.17 (hexane/EtOAc 70:30). $[\alpha]_D$ +61.9 (c 0.59, $CHCl_3$, 23 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (q, $^3J_{HH}$=7.2 Hz, 2H), 3.86–3.72 (m, 1H), 3.56 (d, $^3J_{HH}$=9.5 Hz, 1H), 1.80–1.68 (m, 1H), 1.63–1.49 (m, 2H), 1.41–1.24 (m, 17H), 1.37 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.23 (s, 9H), 0.89

(t, $^3J_{HH}$=7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{CF}$=32.2 Hz), 114.7 (t, $^1J_{CF}$=256.1 Hz), 63.3, 58.9 (t, $^2J_{CF}$=24.9 Hz), 56.9, 31.9, 29.6 (2C), 29.5, 29.3 (2C), 29.1, 28.9, 25.4, 22.7 (3C), 22.7, 14.1, 13.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –110.1 (dd, $^2J_{FF}$=264.3, $^3J_{HF}$=7.5 Hz, 1F), –118.3 (dd, $^2J_{FF}$=264.3, $^3J_{HF}$=16.1 Hz, 1F) ppm. MS (ESI+) (*m/z*) 475 $(M+Na+MeCN)^+$. HRMS (MS+) for $C_{20}H_{39}F_2NNaO_3S$ $(M+Na)^+$ calcd 434.2511, found 434.2513.

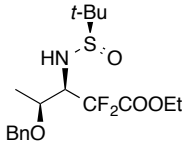
Reaction with sulfinylimine **5S** (100 mg, 0.395 mmol) yielded **13S** (88:12 *dr*). Chromatography (hexane/EtOAc 75:25→65:35) afforded an inseparable mixture of diastereoisomers (68 mg, 0.180 mmol, 46%).

Analytically pure sample of the major diastereoisomer (3*R*,S_S)-ethyl-4-(benzyloxy)-3-(*tert*-butylsulfinamino)-2,2-difluorobutanoate ***ul*-13S** (pale yellow oil) was obtained by HPLC (hexane/EtOAc 70:30): R_f 0.31 (hexane/EtOAc 40:60). $[\alpha]_D$ +33.1 (c 0.62, $CHCl_3$, 19 °C). IR (neat) 3209 (br w), 2982 (br w), 2871 (br w), 1771 (s), 1077 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 4.56 (d, $^2J_{HH}$=11.6 Hz, 1H), 4.49 (d, $^2J_{HH}$=11.6 Hz, 1H), 4.15 (q, $^3J_{HH}$=7.2 Hz, 2H), 4.08–3.95 (m, 2H), 3.92–3.86 (m, 1H), 3.80–3.73 (m, 1H), 1.24 (t, *J*=7.2 Hz, 3H), 1.23 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (t, $^2J_{CF}$=32.2 Hz), 137.2, 128.4 (2C), 127.84, 127.79 (2C), 113.8 (t, $^1J_{CF}$=256.1 Hz), 73.6, 67.6, 62.9, 58.6 (t, $^2J_{CF}$=24.9 Hz), 56.7, 22.4 (3C), 13.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.7 (dd, $^2J_{FF}$=261.8 Hz, $^3J_{HF}$ 8.7 Hz), −115.7 (dd, $^2J_{FF}$=261.8 Hz, $^3J_{HF}$=13.0 Hz) ppm. MS (ESI+) (*m/z*) 400 $(M+Na)^+$. HRMS (MS+) for $C_{17}H_{25}F_2NNaO_4S$ $(M+Na)^+$ calcd 400.1365, found 400.1364.

Reaction with sulfinylimine ***ent*-7S** (100 mg, 0.374 mmol) yielded ***ent*-15S** (94:6 *dr*). Chromatography (PE/Et_2O 40:60→20:80) afforded ***ent-ul*-15S** (80 mg, 0.204 mmol, 54%) as a white solid and ***ent-l*-15S** (4 mg, 0.010 mmol, 3%) as a pale yellow oil.

Major isomer: (3*S*,4*S*,R_s)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate ***ent-ul-*** 

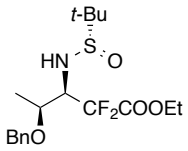
15S: R_f 0.10 (PE/Et_2O 40:60). Mp 109–111 °C. $[\alpha]_D$ –4.2 (c 0.14, $CHCl_3$, 23 °C). IR (neat) 3213 (w, br), 2982 (w), 1771 (s), 1099 (s), 1054 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 4.57 (d, $^2J_{HH}$=11.1 Hz, 1H), 4.38 (d, $^2J_{HH}$=11.1 Hz, 1H), 4.05–3.85 (m, 3H), 3.80 (dq app. as quin, $^3J_{HH}$ 6.3=Hz, 1H), 3.71 (d, $^3J_{HH}$=9.5 Hz, 1H), 1.44 (d, $^3J_{HH}$=6.3 Hz, 3H), 1.24 (s, 9H), 1.16 (t, $^3J_{HH}$=7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0 (t, $^2J_{CF}$=32.2 Hz), 137.4, 128.3 (2C), 128.2 (2C), 127.9, 114.2 (t, $^1J_{CF}$=254.7 Hz), 74.9, 71.4, 63.3 (t, $^2J_{CF}$=23.4 Hz), 62.6, 57.0, 22.5 (3C), 16.4, 13.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –110.0 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=8.6 Hz), –115.2 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=12.9 Hz). MS (ESI+) (*m/z*) 414 $(M+Na)^+$. HRMS (MS+) for $C_{18}H_{27}F_2NNaO_4S$ $(M+Na)^+$ calcd 414.1521, found 414.1525.

Minor isomer: (3*R*,4*S*,R_s)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate ***ent-l-*****15S**: 

R_f 0.20 (PE/Et_2O 40:60). $[\alpha]_D$ –33.5 (c 0.07, $CHCl_3$, 23 °C). IR (neat) 2980 (w), 1770 (m), 1108 (s), 1082 (s), 1026 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 4.56 (d, $^2J_{HH}$=11.1 Hz, 1H), 4.36 (d, $^2J_{HH}$=11.1 Hz, 1H), 4.31 (d, $^3J_{HH}$=10.5 Hz, 1H), 4.09 (qd, $^3J_{HH}$=7.1 Hz, $^2J_{HH}$=6.7 Hz, 1H), 4.07 (qd, $^3J_{HH}$=7.1 Hz, $^2J_{HH}$=6.7 Hz, 1H), 4.00 (qt, $^3J_{HH}$=6.3 Hz, $^3J_{HH}$=1.7 Hz, 1H), 3.74 (dddd, $^3J_{HF}$=12.4 Hz, $^3J_{HH}$=10.5 Hz, $^3J_{HF}$=8.7 Hz, $^3J_{HH}$=1.8 Hz, 1H), 1.29 (d, $^3J_{HH}$=6.3 Hz, 3H), 1.27 (s, 9H), 1.20 (t, $^3J_{HH}$=7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 128.3 (2C), 127.8 (3C), 113.6 (t, $^1J_{CF}$=257.6 Hz), 72.1 (d, $^3J_{CF}$=2.9 Hz), 71.1, 63.0 (t, $^2J_{CF}$=24.9 Hz), 63.0, 57.2, 22.9 (3C), 16.6, 13.7 ppm (The C=O signal was not observed). ^{19}F NMR (282 MHz, $CDCl_3$) δ –108.0 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=8.7 Hz), –114.6 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=12.4 Hz) ppm. MS (ESI) (*m/z*) 455 $(M+Na+MeCN)^+$. HRMS (ESI) for $C_{18}H_{27}F_2NNaO_4S$ $(M + Na)^+$ calcd 414.1521, found 414.1509.

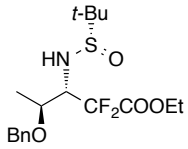
Reaction with sulfinylimine ***ent*-7R** (100 mg, 0.374 mmol) yielded ***ent*-15R** (54:46 *dr*). Chromatography (PE/Et_2O 40:60→20:80) afforded ***ent-ul*-15R** (37 mg, 0.095 mmol, 25%) and ***ent-l*-15R** (31 mg, 0.079 mmol, 21%).

Major isomer: (3*R*,4*S*,S_s)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate ***ent-ul*-15R**



(pale yellow oil): R_f 0.38 (PE/Et_2O 20:80). $[\alpha]_D$ +30.0 (c 0.62, $CHCl_3$, 23 °C). IR (neat) 3353 (w, br), 2979 (w), 1765 (m), 1079 (s), 1021 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 4.60 (d, $^2J_{HH}$=11.0 Hz, 1H), 4.33 (d, $^2J_{HH}$=11.0 Hz, 1H), 4.30 (d, $^3J_{HH}$=9.1 Hz, 1H), 4.09–3.98 (m, 3H), 3.66 (dddd, $^3J_{HF}$=12.8, $^3J_{HH}$=9.1 Hz, $^3J_{HF}$=8.9 Hz, $^3J_{HH}$=0.9 Hz, 1H), 1.42 (d, $^3J_{HH}$=6.4 Hz, 3H), 1.24 (s, 9H), 1.16 (t, $^3J_{HH}$=7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (dd, $^2J_{CF}$=33.7, 30.7 Hz), 137.5, 128.3 (2C), 127.8 (2C), 127.7, 113.8 (t, $^1J_{CF}$=255.4 Hz), 70.7, 70.4 (d, $^3J_{CF}$=2.9 Hz), 64.1 (dd, $^2J_{CF}$=27.8 Hz, $^2J_{CF}$=23.4 Hz), 62.7, 56.8, 22.5 (3C), 16.6, 13.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –109.9 (dd, $^2J_{FF}$=257.9 Hz, $^3J_{HF}$=8.9 Hz), –114.7 (dd, $^2J_{FF}$=257.9 Hz, $^3J_{HF}$=12.8 Hz) ppm. MS (ESI+) (*m*/*z*) 414 $(M+Na)^+$. HRMS (MS+) for $C_{18}H_{27}F_2NNaO_4S$ $(M+Na)^+$ calcd 414.1521, found 414.1526.

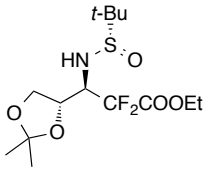
Minor isomer: (3*S*,4*S*,S_s)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate ***ent-l*-15R**



(pale yellow oil): R_f 0.22 (PE/Et_2O 20:80). $[\alpha]_D$ +37.7 (c 0.53, $CHCl_3$, 23 °C). IR (neat) 3213 (w, br), 2981 (w), 1770 (m), 1097 (s), 1055 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H), 4.51 (d, $^2J_{HH}$=11.2 Hz, 1H), 4.39 (d, $^2J_{HH}$=11.2 Hz, 1H), 4.08–3.92 (m, 3H), 3.76–3.68 (m, 1H), 3.68 (d, $^3J_{HH}$=9.3 Hz, 1H), 1.32 (d, $^3J_{HH}$=6.1 Hz, 3H), 1.24 (s, 9H), 1.18 (t, $^3J_{HH}$=7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (dd, $^2J_{CF}$=32.2 Hz, $^2J_{CF}$=30.7 Hz), 137.4, 128.3 (2C), 128.0 (2C), 127.8, 113.8 (t, $^1J_{CF}$=254.7 Hz), 73.9, 71.0, 62.8, 62.7 (dd, $^2J_{CF}$=23.4 Hz, $^2J_{CF}$=22.0 Hz), 57.1, 22.7 (3C), 16.6, 13.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –109.6 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=8.6 Hz), –117.3 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=17.2 Hz) ppm. MS (ESI) (*m*/*z*) 455 $(M+Na+MeCN)^+$. HRMS (MS+) for $C_{18}H_{27}F_2NNaO_4S$ $(M+Na)^+$ calcd 414.1521, found 414.1524.

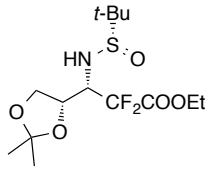
Reaction with sulfinylimine **8S** (109 mg, 0.467 mmol) yielded ***ul*-16S** as a single diastereoisomer. Chromatography (PE/EtOAc 70:30→50:50) afforded ***ul*-16S** (103 mg, 0.288 mmol, 62%) as a white solid.

Major isomer: (3*R*,4*S*,S_S)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-



difluoropentanoate ***ul*-16S**: R_f 0.26 (PE/EtOAc 50:50). Mp 88–90 °C. $[\alpha]_D$ +30.3 (*c* 0.29, $CHCl_3$, 23 °C). IR (neat) 3194 (w), 2986 (w), 1777 (m), 1761 (m), 1053 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38–4.11 (m, 5H), 3.96 (dddd, $^3J_{HF}$=17.4 Hz, $^3J_{HH}$=8.7 Hz, $^3J_{HF}$=8.2 Hz, $^3J_{HH}$=7.2 Hz, 1H), 3.54 (d, $^3J_{HH}$=8.7 Hz, 1H), 1.39 (s, 3H), 1.34 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.29 (s, 3H), 1.21 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (t, $^2J_{CF}$=30.8 Hz), 113.8 (dd, $^1J_{CF}$=256.4 Hz, $^1J_{CF}$=252.5 Hz), 110.6, 73.6, 66.8, 63.0, 61.1 (dd, $^2J_{CF}$=22.6 Hz, $^2J_{CF}$=21.5 Hz), 57.1, 25.9, 24.9, 22.4 (3C), 13.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –110.0 (dd, $^2J_{FF}$=262.6 Hz, $^3J_{HF}$=8.2 Hz), –119.4 (dd, $^2J_{FF}$=262.6 Hz, $^3J_{HF}$=17.4 Hz) ppm. MS (ESI+) (*m*/*z*) 421 $(M+Na+MeCN)^+$. HRMS (MS+) for $C_{14}H_{25}F_2NNaO_5S$ $(M+Na)^+$ calcd 380.1314, found 380.1312.

Minor isomer: (3*S*,4*S*,S_S)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-

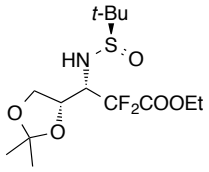


difluoropentanoate ***l*-16S** (isolated from an unselective reaction, pale yellow oil): $[\alpha]_D$ +6.2 (*c* 0.17, $CHCl_3$, 23 °C). IR (neat) 2991 (w), 1770 (s), 1137 (s), 1123 (s), 1107 (s) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (ddd, $^3J_{HH}$=7.1 Hz, $^3J_{HH}$=6.1 Hz, $^3J_{HH}$=2.2 Hz, 1H), 4.45–4.32 (m, 2H), 4.11 (dd, $^2J_{HH}$=8.2 Hz, $^3J_{HH}$=7.1 Hz, 1H), 4.14 (d, $^3J_{HH}$=10.4 Hz, 1H), 3.85 (dddd, $^3J_{HF}$=16.3 Hz, $^3J_{HH}$=10.4 Hz, $^3J_{HF}$=6.1 Hz, $^3J_{HH}$=2.2 Hz, 1H), 3.80 (dd, $^2J_{HH}$=8.2 Hz, $^3J_{HH}$=6.1 Hz, 1H), 1.44 (s, 3H), 1.38 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.33 (s, 3H), 1.26 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (t, $^2J_{CF}$=31.4 Hz), 113.5 (dd, $^1J_{CF}$=261 Hz, $^1J_{CF}$=256 Hz), 110.2, 72.1 (d, $^3J_{CF}$=3.3 Hz), 66.1, 63.5, 59.4 (t, $^2J_{CF}$=24.8 Hz), 57.3, 26.1, 24.4, 22.6 (3C), 13.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –107.0 (dd,

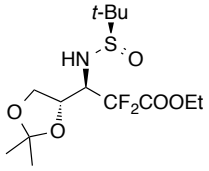
$^2J_{FF}$=265.7 Hz, $^3J_{HF}$=6.1 Hz), –117.9 (dd, $^2J_{FF}$=265.7 Hz, $^3J_{HF}$=16.3 Hz) ppm. HRMS (MS+) for $C_{14}H_{25}F_2NNaO_5S$ $(M+Na)^+$ calcd 380.1314, found 380.1305.

Reaction with sulfinylimine **8R** (150 mg, 0.643 mmol) yielded **16R** (88:12 *dr*). Chromatography (PE/EtOAc 75:25→70:30) afforded ***ul*-16R** (120 mg, 0.336 mmol, 52%) and ***l*-16R** (15 mg, 0.042 mmol, 7%) as white solids.

Major isomer: (3*S*,4*S*,R_S)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-



difluoropentanoate ***ul*-16R**: R_f 0.50 (hexane/EtOAc 50:50). Mp 84–86 °C. $[\alpha]_D$ −62.5 (c 0.81, $CHCl_3$, 21 °C). IR (neat) 3313 (br w), 2985 (br m), 1771 (s), 1077 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.54−4.40 (m, 1H), 4.38−4.25 (m, 3H), 4.15 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=7.8 Hz, 1H), 4.10 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=6.6 Hz, 1H), 3.91−3.77 (m, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.36 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.24 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (t, $^2J_{CF}$=30.7 Hz), 113.9 (dd, $^1J_{CF}$=259.1 Hz, $^1J_{CF}$=254.7 Hz), 110.4, 70.8 (d, $^3J_{CF}$=2.9 Hz), 66.2, 63.0, 57.9 (t, $^2J_{CF}$=25.6 Hz), 56.7, 26.2, 25.6, 22.5 (3C), 13.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.9 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=8.6 Hz), –118.1 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=17.2 Hz) ppm. MS (ESI+) (*m*/*z*) 421 ((M+Na+MeCN)$^+$. HRMS (MS+) for $C_{14}H_{26}F_2NO_5S$ $(M+H)^+$ calcd 358.1500, found 358.1494.

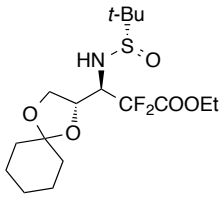


Minor isomer: (3*R*,4*S*,R_S)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate ***l*-16R**: R_f 0.32 (hexane/EtOAc 50:50). Mp 86–88 °C . $[\alpha]_D$ −22.6 (c 0.06, $CHCl_3$, 22 °C). IR (neat) 3205 (br w), 2986 (br m), 1775 (s), 1065 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.43−4.22 (m, 3H), 4.14 (dd, $^2J_{HH}$=8.6 Hz, $^3J_{HH}$=6.4 Hz, 1H), 4.07−3.94 (m, 1H), 3.88 (dd, $^2J_{HH}$=8.6 Hz, $^3J_{HH}$=6.3 Hz, 1H), 3.65 (d, $^3J_{HH}$=9.0 Hz, 1H), 1.39 (s, 3H), 1.38 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.33 (s, 3H), 1.25 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (t, $^2J_{CF}$=30.8 Hz), 113.6 (dd, $^1J_{CF}$=257.5, 253.8 Hz), 110.5, 73.7 (d, $^3J_{CF}$=2.9 Hz), 67.1, 63.3, 61.0 (t, $^2J_{CF}$=22.0 Hz), 57.2, 26.1, 25.1, 22.6 (3C), 13.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.1 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$

8.6 Hz), –118.1 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=12.9 Hz) ppm. MS (ESI+) (*m/z*) 421 ((M+Na+MeCN)$^+$, 100). HRMS (MS+) for $C_{14}H_{26}F_2NO_5S$ (M+H)$^+$ calcd 358.1500, found 358.1498.

Reaction with sulfinylimine **9S** (100 mg, 0.366 mmol) yielded ***ul*-17S** (single diastereoisomer). Chromatography (PE/EtOAc 65:35→50:50) afforded ***ul*-17S** (75 mg, 0.189 mmol, 52%).

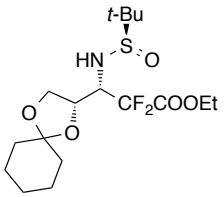
(3*R*,4*S*,S_S)-Ethyl-4,5-cyclohexylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate ***ul*-17S**



(white solid): R_f 0.23 (PE 40-60 °C/EtOAc 50:50). Mp 112–116 °C. $[\alpha]_D$ +28.3 (c 0.56, $CHCl_3$, 23 °C). IR (neat) 3203 (br, w), 2937 (m), 1761 (m), 1092 (m), 1050 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37–4.06 (m, 5H), 3.96 (dddd, $^3J_{HF}$=17.2 Hz, $^3J_{HF}$=8.6 Hz, $^3J_{HH}$=8.5 Hz, $^3J_{HH}$=7.3 Hz, 1H), 3.54 (d, $^3J_{HH}$=8.5 Hz, 1H), 1.70–1.45 (m, 8H), 1.44–1.28 (m, 2H), 1.35 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.21 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (t, $^2J_{CF}$=30.7 Hz), 113.9 (dd, $^1J_{CF}$=256.1 Hz, $^1J_{CF}$=251.8 Hz), 111.3, 73.2, 66.5, 62.9, 61.1 (t, $^2J_{CF}$=22.0 Hz), 57.1, 35.6, 34.2, 24.9, 23.8, 23.6, 22.4 (3C), 13.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –109.5 (dd, $^2J_{FF}$=264.3 Hz, $^3J_{HF}$=8.6 Hz), –118.9 (dd, $^2J_{FF}$=264.3 Hz, $^3J_{HF}$=17.2 Hz) ppm. MS (ESI+) (*m/z*) 461 (M+Na+MeCN)$^+$. HRMS (MS+) for $C_{17}H_{30}F_2NO_5S$ (M+H)$^+$ calcd 398.1807, found 398.1804.

Reaction with sulfinylimine **9R** (100 mg, 0.366 mmol) yielded **17R** (81:19 *dr*). Chromatography (PE/EtOAc 80:20→65:35) afforded ***ul*-17R** (70 mg, 0.176 mmol, 48%) and ***l*-17R** (12 mg, 0.030 mmol, 8%) as white solids.

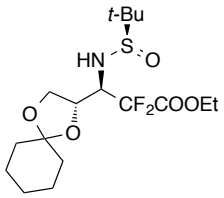
Major isomer: (3*S*,4*S*,R_S)-ethyl-4,5-cyclohexylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-



difluoropentanoate ***ul*-17R**: R_f 0.21 (PE/EtOAc 65:35). Mp 72–75 °C. $[\alpha]_D$ −29.9 (c 0.68, $CHCl_3$, 21 °C). IR (neat) 3311 (br w), 2935 (m), 1770 (s), 1075 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (t, $^3J_{HH}$=7.2 Hz, 1H), 4.39–4.24 (m, 3H), 4.16–4.07 (m, 2H), 3.90–3.76 (m, 1H), 1.70–1.51 (m, 8H), 1.46–1.33 (m, 2H), 1.37 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.25 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (t, $^2J_{CF}$=30.7 Hz), 113.9 (t, $^1J_{CF}$=259.1 Hz), 111.0, 70.5

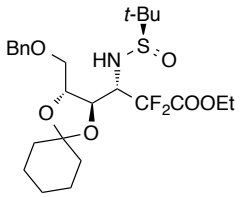
(d, $^3J_{CF}$=2.9 Hz), 65.9, 63.0, 58.0 (t, $^2J_{CF}$=26.3 Hz), 56.7, 35.7, 35.4, 25.0, 23.9, 23.7, 22.5 (3C), 13.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –108.9 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=8.6 Hz), –117.8 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=17.2 Hz) ppm. MS (ESI+) (*m*/*z*) 461 $(M+Na+MeCN)^+$. HRMS (MS+) for $C_{17}H_{30}F_2NO_5S$ $(M+H)^+$ calcd 398.1807, found 398.1808.

Minor isomer: (3*R*,4*S*,R_S)-ethyl-4,5-cyclohexylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-



difluoropentanoate ***l*-17R**: R_f 0.12 (PE/EtOAc 65:35). Mp 122–124 °C $[\alpha]_D$ –39.0 (c 0.50, $CHCl_3$, 19 °C). IR (neat) 3204 (br w), 2937 (m), 1762 (s), 1053 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (dq, $^2J_{HH}$=10.7, $^3J_{HH}$=7.2 Hz, 1H), 4.30 (dq, $^2J_{HH}$=10.7, $^3J_{HH}$=7.2 Hz, 1H), 4.25–4.18 (m, 1H), 4.15–4.08 (m, 1H), 3.98 (dddd app. ddt, $^3J_{HF}$=16.1, $^3J_{HH}$=9.1, $^3J_{HF}$=$^3J_{HH}$=8.6 Hz, 1H), 3.83 (dd, $^3J_{HH}$=8.6, 6.3 Hz, 1H), 3.67 (d, $^3J_{HH}$=9.1 Hz, 1H), 1.63–1.48 (m, 8H), 1.43–1.31 (m, 2H), 1.36 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.23 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (t, $^2J_{CF}$=30.7 Hz), 113.7 (dd, $^1J_{CF}$=256.1 Hz, $^1J_{CF}$ 253.2 Hz), 111.2, 73.2 (br. s), 66.8, 63.2, 61.1 (t, $^2J_{CF}$=22.0 Hz), 57.1, 35.8, 34.4, 24.9, 23.8, 23.6, 22.6 (3C), 13.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –108.6 (dd, $^2J_{FF}$=262.8, $^3J_{HF}$=8.6 Hz), –118.3 (d, $^2J_{FF}$=262.2, $^3J_{HF}$=16.1 Hz) ppm. MS (ESI+) (*m*/*z*) 461 (M+Na+MeCN. HRMS (MS+) for $C_{17}H_{30}F_2NO_5S$ $(M+H)^+$ calcd 398.1807, found 398.1814.

Reaction with sulfinylimine ***ent*-10S** (2.06 g, 5.24 mmol) yielded ***ent-ul*-18S** (single diastereoisomer). Chromatography (PE/EtOAc 75:25→60:40) afforded ***ent-ul*-18S** (1.81 g, 3.50 mmol, 67%). (3*S*,4*R*,5*R*,R_S)-Ethyl-[6-(benzyloxy)-3-(*t*-butylsulfinylamino)-4,5-(cyclohexylidenedioxy)-2,2-

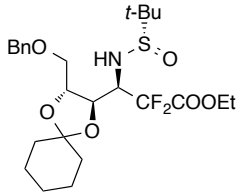


difluorohexanoate ***ent-ul*-18S** (pale yellow oil): R_f 0.35 (PE/EtOAc 50:50). $[\alpha]_D$ +43.2 (c 0.35, $CHCl_3$, 22 °C). IR (neat) 3244 (w), 2936 (m), 2360 (m), 1774 (m), 1759 (m), 1060 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 4.62 (d, $^3J_{HH}$=6.4 Hz, 1H), 4.56 (s, 2H), 4.49 (ddd, $^3J_{HH}$=8.8 Hz, $^3J_{HH}$=6.8 Hz, $^3J_{HH}$=4.4 Hz, 1H), 4.32 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.1 Hz, 1H), 4.28 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.1 Hz, 1H), 4.13 (dd, $^3J_{HH}$=8.5 Hz,

$^3J_{HH}$=6.8 Hz, 1H), 3.99 (dddd, $^3J_{HF}$=17.2 Hz, $^3J_{HH}$=8.5 Hz, $^3J_{HF}$=7.5 Hz, $^3J_{HH}$=6.4 Hz, 1H), 3.88 (dd, $^2J_{HH}$=8.8 Hz, $^3J_{HH}$=4.4 Hz, 1H), 3.38 (dd app. t, $^2J_{HH}$=8.8 Hz, $^3J_{HH}$ 8.8 Hz, 1H), 1.74–1.61 (m, 1H), 1.61–1.45 (m, 7H), 1.36 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.44–1.26 (m, 2H), 1.08 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{CF}$=30.7 Hz), 136.9, 128.6 (2C), 128.1 (3C), 114.0 (dd, $^1J_{CF}$=257.6 Hz, $^1J_{CF}$=251.8 Hz), 111.6, 76.5, 76.2, 73.9, 71.1, 62.8, 61.7 (t, $^2J_{CF}$=22.0 Hz), 56.4, 36.3, 35.7, 24.9, 23.7, 23.6, 22.5 (3C), 13.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –110.8 (dd, $^2J_{FF}$=260.0 Hz, $^3J_{HF}$=7.5 Hz), –121.4 (dd, $^2J_{FF}$=260.0 Hz, $^3J_{HF}$=17.2 Hz) ppm. MS (ESI+) (*m/z*) 540 $(M+Na)^+$. HRMS (MS+) for $C_{25}H_{38}F_2NO_6S$ $(M+H)^+$ calcd 518.2382, found 518.2377.

Reaction with sulfinylimine ***ent*-10R** (100 mg, 0.254 mmol) yielded ***ent*-18R** (60:40 *dr*). Chromatography (PE/EtOAc 75:25→70:30) afforded ***ent-ul*-18R** (41 mg, 0.079 mmol, 31%) and ***ent-l*-18R** (22 mg, 0.043 mmol, 17%).

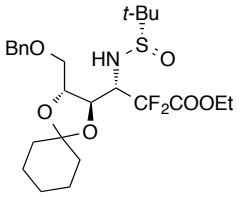
Major isomer: (3*R*,4*R*,5*R*,S_S)-ethyl-6-(benzyloxy)-3-(*t*-butylsulfinylamino)-4,5-(cyclohexylidenedioxy)-2,2-difluorohexanoate ***ent-ul*-18R** (pale yellow oil):



R_f 0.37 (PE/EtOAc 70:30). $[\alpha]_D$ +50.8 (*c* 0.53, $CHCl_3$, 20 °C). IR (neat) 2936 (s), 2863 (w), 1773 (m), 1760 (m), 1073 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H), 4.63 (d, $^2J_{HH}$=12.1 Hz, 1H), 4.59 (d, $^2J_{HH}$=12.1 Hz, 1H), 4.51–4.44 (m, 2H), 4.30 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.2 Hz, 1H), 4.26 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.2 Hz, 1H), 4.20 (d, $^3J_{HH}$=8.7 Hz, 1H), 4.05 (ddd, $^3J_{HF}$=17.2 Hz, $^3J_{HH}$=8.7 Hz, $^3J_{HH}$=7.5 Hz, 1H), 3.78 (dd, $^2J_{HH}$=10.1 Hz, $^3J_{HH}$=4.2 Hz, 1H), 3.62 (dd, $^2J_{HH}$=10.1 Hz, $^3J_{HH}$=6.4 Hz, 1H), 1.77–1.47 (m, 8H), 1.44–1.30 (m, 2H), 1.33 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.24 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (t, $^2J_{CF}$=33.7 Hz), 137.9, 128.3 (2C), 127.6 (3C), 114.0 (dd, $^1J_{CF}$=259.1 Hz, $^1J_{CF}$=254.7 Hz), 110.8, 74.3, 74.2 (d, $^3J_{CF}$=2.9 Hz), 73.6, 69.5, 62.9, 57.7 (t, $^2J_{CF}$=24.9 Hz), 56.7, 36.6, 36.1, 24.9, 23.8, 23.7, 22.5 (3C), 13.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –109.1 (dd, $^2J_{FF}$=257.9 Hz, $^3J_{HF}$=7.5 Hz), –117.9 (dd, $^2J_{FF}$=257.9 Hz,

$^3J_{HF}$=17.2 Hz) ppm. MS (ESI+) (*m/z*) 540 $(M+Na)^+$. HRMS (MS+) for $C_{25}H_{38}F_2NO_6S$ $(M+H)^+$ calcd 518.2382, found 518.2378.

Minor isomer: (3*S*,4*R*,5*R*,S_S)-ethyl-6-(benzyloxy)-3-(*t*-butylsulfinylamino)-4,5- (cyclohexylidenedioxy)-



2,2-difluorohexanoate ***ent-l*-18R** (pale yellow oil): R_f 0.18 (PE/EtOAc 70:30). $[\alpha]_D$ +28.3 (c 0.72, $CHCl_3$, 20 °C). IR (neat) 2936 (s), 2863 (w), 1773 (m), 1760 (m), 1057 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H), 4.57 (s, 2H), 4.36 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.2 Hz, 1H), 4.31 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.2 Hz, 1H), 4.30–4.23 (m, 1H), 4.09–3.95 (m, 2H), 3.83 (d, $^3J_{HH}$=9.2 Hz, 1H), 3.63 (dd, $^2J_{HH}$=10.0 Hz, $^3J_{HH}$=5.3 Hz, 1H), 3.58 (dd, $^2J_{HH}$=10.0 Hz, $^3J_{HH}$=4.9 Hz, 1H), 1.68–1.47 (m, 8H), 1.41–1.32 (m, 2H), 1.36 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.15 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (t, $^2J_{CF}$=31.1 Hz), 137.6, 128.5 (2C), 128.0 (2C), 127.9, 113.8 (dd, $^1J_{CF}$=256.5 Hz, $^1J_{CF}$=255.0 Hz), 111.4, 77.5, 76.0 (t, $^3J_{CF}$=2.6 Hz), 73.7, 71.1, 63.2 , 60.7 (t, $^2J_{CF}$=22.7 Hz), 57.2, 36.4, 36.3, 25.0, 23.8, 23.7, 22.5 (3C), 13.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ –108.4 (d, $^2J_{FF}$=262.2 Hz), –116.8 (d, $^2J_{FF}$=262.2 Hz) ppm. MS (ESI+) (*m/z*) 540 $(M+Na)^+$. HRMS (MS+) for $C_{25}H_{37}F_2NNaO_6S$ $(M+Na)^+$ calcd 540.2202, found 540.2192.

Acknowledgement. The European Community (INTERREG IVa Channel Programme, IS:CE-Chem, project 4061) is thanked for financial support.

Supporting Information: Characterization data for known compounds, copies of ^{19}F NMR spectra of the crude Honda-Reformatsky reaction mixtures, copies of ^{1}H, ^{13}C, ^{19}F NMR spectra of all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org/.

References

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