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. These include the pharmaceutical and agrochemical industries – around 20% of the commercially available pharmaceuticals and 30% of agrochemicals are fluorinated, and performance materials, such as liquid crystals. Given the abundance of amine containing bioactive compounds, their fluorination has received great attention. The β-position of amino groups is often considered for fluorination given the resulting effect on their pKa(H) value and lipophilicity. Fluorination will also have an impact on the amine hydrogen bonding properties, and will induce potentially strong conformational effects.

The conformational properties and biological activities of β-amino acids have received great attention, including the corresponding α,α-difluoro-β-amino acids. Their synthesis using direct C–C bond formations with fluorinated building blocks usually involve Reformatsky reaction of BrCF₂COOEt to imine derivatives (or their equivalents). 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 and imines derived from (R)-phenyl glycinol. 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, we are not aware of examples of Reformatsky reactions (either with or with BrCH₂COOEt) on these types of sulfinylimines. Only a few examples were found where 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, while a complex C-glycosyl derived imine gave complete syn-selectivity.
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. Furthermore, Ellman has recently described the addition of a benzyl zinc reagent to either diastereomer of the t-butanbesulfinyl imine derived from (R)-glyceraldehyde acetonide, which for the matched case proceeded with virtually complete stereoselectivity. Herein we describe a study of the Reformatsky reaction using I 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. As expected, 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-butanbesulfinylimines.
The Reformatsky reaction was first investigated by a short optimization effort using sulfimine 8S, which was predicted to proceed with matched double diastereoselection.\textsuperscript{30} Promotion by indium\textsuperscript{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\textsubscript{2}O or toluene as co-solvent gave similar results (not shown). Zn activation by DMSO/TMSCl\textsuperscript{35} failed to induce reaction (entry 5). Pleasingly, using Et\textsubscript{2}Zn under Honda-Reformatsky conditions, which employs
the Wilkinson catalyst to promote Zn insertion,\textsuperscript{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)\textsuperscript{38} or of Et$_2$Zn by Me$_2$Zn (entry 9) was not possible.

Table 2. Optimisation of the Reaction.\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>1 (equiv)</th>
<th>metal (equiv)</th>
<th>additive (equiv)</th>
<th>d.r$^b$</th>
<th>yields (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>In (2)</td>
<td>-</td>
<td>-</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Zn (3)</td>
<td>-</td>
<td>72:28</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>Zn (4)</td>
<td>-</td>
<td>85:15</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>Zn$^d$ (4)</td>
<td>-</td>
<td>75:25</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>Zn$^e$ (4)</td>
<td>-</td>
<td>-</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>Et$_2$Zn (1.5)</td>
<td>RhCl(PPh$_3$)$_3$</td>
<td>&gt;95:5</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>Et$_2$Zn (2)</td>
<td>RhCl(PPh$_3$)$_3$</td>
<td>&gt;95:5</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>Et$_2$Zn (1.5)</td>
<td>NiCl$_2$(PPh$_3$)$_2$</td>
<td>-</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>1.1</td>
<td>Me$_2$Zn (3)</td>
<td>RhCl(PPh$_3$)$_3$</td>
<td>-</td>
<td>NR</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The prefix \textit{l} (like) indicates that the sulfinyl group and the newly formed amine stereocentre have the same absolute configuration (and otherwise for \textit{ul} (unlike)). The suffix \textit{R} or \textit{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.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>imine</th>
<th>major product</th>
<th>yield (%)</th>
<th>d.r. (ul:l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>3S</td>
<td>ul-11S</td>
<td>64</td>
<td>53:47</td>
</tr>
<tr>
<td>2</td>
<td>C_{11}H_{23}</td>
<td>4S</td>
<td>ul-12S</td>
<td>58</td>
<td>53:47</td>
</tr>
<tr>
<td>3</td>
<td>BnO</td>
<td>5S</td>
<td>ul-13S</td>
<td>46</td>
<td>88:12</td>
</tr>
<tr>
<td>4</td>
<td>BnO</td>
<td>6S</td>
<td>-</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>5e</td>
<td>7S</td>
<td>7S</td>
<td>ul-15S</td>
<td>57</td>
<td>94:6</td>
</tr>
<tr>
<td>6e</td>
<td>BnO</td>
<td>7R</td>
<td>ul-15R</td>
<td>46</td>
<td>54:46</td>
</tr>
<tr>
<td>7</td>
<td>8S</td>
<td>8S</td>
<td>ul-16S</td>
<td>62</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>8</td>
<td>8R</td>
<td>8R</td>
<td>ul-16R</td>
<td>59</td>
<td>88:12</td>
</tr>
<tr>
<td>9</td>
<td>9S</td>
<td>9S</td>
<td>ul-17S</td>
<td>52</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>10</td>
<td>9R</td>
<td>9R</td>
<td>ul-17R</td>
<td>56</td>
<td>81:19</td>
</tr>
<tr>
<td>11e</td>
<td>BnO</td>
<td>10S</td>
<td>ul-18S</td>
<td>62 (67)</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>12e</td>
<td>10R</td>
<td>10R</td>
<td>ul-18R</td>
<td>48</td>
<td>60:40</td>
</tr>
</tbody>
</table>

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-Reformatsky conditions (entries 1,2). We also observed slight variations in diastereoselectivity...
depending on the age of the Et₂Zn 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 Staas¹⁸ 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 benzyloxyethyl-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 ZnEt₂/RhCl(PPh₃)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. Their benzyl zinc reagent was synthesized from the corresponding benzyl chloride using ZnCl₂/Mg/LiCl (Knochel conditions). The benzyl zinc reagent was synthesized from the corresponding benzyl chloride using ZnCl₂/Mg/LiCl (Knochel conditions).

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), which both predict the observed Si-face attack. In contrast, the cyclic “Cram model” TS-3, 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. 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, and which successfully explains the Staas and Soloshonok results (as well as for Reformatsky reactions using BrCH₂COOEt). However, given it predicts Re face attack (for an (S)-configured sulfinylimine), it is not consistent with our findings. Equally, TS-5, 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). In contrast, the Barrow chelation model TS-6, 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.\textsuperscript{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,\textsuperscript{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\textsuperscript{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).\textsuperscript{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\(_2\)Cl\(_2\) 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).

\((S,E)-N-(\text{propylidene})-2\text{-methyl}-2\text{-propanesulfimide} \ (3S)^{49}\)

\[
\begin{array}{c}
\text{Propionaldehyde (0.100 g, 1.72 mmol), (S)-2-methyl-2-propanesulfimide (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\(_3\)) \(\delta\) 8.11 (t, 3\(J_{HH}\)=4.3 Hz, 1H), 2.55 (dq, 3\(J_{HH}\)=7.4 Hz, 3\(J_{HH}\)=4.3 Hz, 2H), 1.20 (s, 9H), 1.20 (t, 3\(J_{HH}\)=7.4 Hz, 3H) ppm. 13C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.3, 56.5, 29.5, 22.3 (3C), 9.6 ppm. NMR spectra correspond to the reported data for ent-3S.\(^{49}\)
\end{array}
\]

\((S,E)-N-[\text{dodecylidene}]-2\text{-methyl}-2\text{-propanesulfimide} \ (4S)\)

\[
\begin{array}{c}
\text{Dodecanal (0.30 mL, 0.249 g, 1.34 mmol), (S)-2-methyl-2-propanesulfimide (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\(_3\)) \(\delta\) 8.07 (t, 3\(J_{HH}\)=4.7 Hz, 1H), 2.52 (dt, 3\(J_{HH}\)=7.4 Hz, 3\(J_{HH}\)=4.7 Hz, 2H), 1.20–1.60 (m, 2H), 1.51–1.24 (m, 16H), 1.20 (s, 9H), 0.89 (t, 3\(J_{HH}\)=7.1 Hz, 3H) ppm. 13C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.8, 56.5, 36.1, 31.9, 29.6 (2C), 29.5, 29.3
\end{array}
\]
To benzylxyacetaldehyde \( ^{50} \) (0.250 g, 1.67 mmol) in CH\(_2\)Cl\(_2\) (3.5 mL) were added \((S)-2-\text{methyl}-2-\text{propanesulfinamide} \) (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\(^\circ\) to afford the desired crude product. Purification over a short pad of silica eluting with PE/EtOAc 75:25 yielded \(\mathbf{5S} \) (0.371 g, 1.46 mmol, 88%) as a pale yellow oil. \( R_f \) 0.21 (hexane/ethyl acetate 70:30). \( [\alpha]_D^{26} +161.6 \) (c 0.09, CHCl\(_3\), 26 °C), lit. \( [\alpha]_D^{51} \) –212 (c 1.0, CHCl\(_3\), 23 °C).

\( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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 \(\text{ent-5S}^\text{51} \).

\( ^{-}(R,S,E)-N-[2-(\text{Benzyloxy})-2-\text{methylpropyliendene}] 2-\text{methyl}-2-\text{propanesulfinamide (ent-7S)}^\text{33} \)

(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,E)-N-[2-\text{Benzyloxyethylidene}] 2-\text{methyl}-2-\text{propanesulfinamide (5S)}\\n\begin{align*}
\text{N} & \quad \text{S} \\
\text{Bu} & \quad \text{O} \\
\text{BnO} & \quad \text{O}
\end{align*}\\

\(\text{N} \quad \text{S} \\
\text{Bu} & \quad \text{O} \\
\text{BnO} & \quad \text{O}
\end{align*}

\begin{align*}
\text{N} & \quad \text{S} \\
\text{Bu} & \quad \text{O} \\
\text{BnO} & \quad \text{O}
\end{align*}
(2S)–2-Benzyloxypropanal\textsuperscript{52} (0.150 g, 0.914 mmol), (R)–2-methyl–2-propanesulfonamide (0.122 g, 1.01 mmol) and Ti(OEt)\textsubscript{4} (0.625 g, 2.74 mmol) yielded ent-7S (0.200 g, 0.748 mmol, 82%) as a pale yellow oil. R\textsubscript{f} 0.60 (hexane/EtOAc 50:50). [\alpha]_D -222 (c 0.52, EtOH, 22 °C). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 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. \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 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.\textsuperscript{33}

(S\textsubscript{3},E)-N–[(2S)-2-(Benzyloxy)propylidene]-2-methyl-2-propanesulfonamide (ent-7R)

(2S)–2-Benzyloxypropanal\textsuperscript{52} (0.150 g, 0.914 mmol), (S)–2-methyl–2-propanesulfonamide (0.116 g, 0.959 mmol) and Ti(OEt)\textsubscript{4} (0.833 g, 3.65 mmol) yielded ent-7R (0.173 g, 0.647 mmol, 71%) as a pale yellow oil. R\textsubscript{f} 0.40 (hexane/EtOAc 50:50). [\alpha]_D +67.3 (c 0.53, EtOH, 22 °C). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 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), 4.35 (dq, \(^3J_{HH}=6.7\) Hz, \(^3J_{HH}=4.5\) Hz, 1H), 1.41 (d, \(^3J_{HH}=6.7\) Hz, 3H), 1.24 (s, 9H) ppm. \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 170.5, 137.6, 128.5, 127.9, 127.8, 76.3, 71.6, 56.9, 22.5, 18.5 ppm. NMR spectra correspond to the reported data.\textsuperscript{33}

(R\textsubscript{3},E)-N–[(2S)-2,3-(isopropylidenedioxy)propylidene]-2-methyl-2-propanesulfonamide (8R)

2,3–O,O–Isopropylidene–D–glyceraldehyde\textsuperscript{53} (0.500 g, 3.84 mmol), (R)–2–methyl–2–propanesulfonamide (0.489 g, 4.03 mmol) and Ti(OEt)\textsubscript{4} (4.38 g, 19.2 mmol) yielded 8R (0.771 g, 3.30 mmol, 86%) as a pale yellow oil. R\textsubscript{f} 0.21 (hexane/EtOAc 70:30). [\alpha]_D -198.6 (c 0.84, CHCl\textsubscript{3}, 26 °C). IR (neat) 2984 (m), 2873 (m), 1626 (s), 1060 (s) cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.02 (d, \(^3J_{HH}=4.5\) Hz, 1H), 4.83 (dd, \(^3J_{HH}=7.6\) 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$_3$) $\delta$ 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$_3$S (M+Na)$^+$ calcd 256.0983, found 256.0978. NMR spectra correspond to the reported data.$^{30}$

$(S,S,E)-N-[(2S)-2, 3-\text{(isopropilenedioxy)propylidene}]2\text{-methyl-2-propanesulfinamide (8S)}$

\[
\text{\begin{tikzpicture}
\node[below] at (0,0) {\text{2,3-O, O-Isopropylidene-d-glyceraldehyde}};\node[below] at (0,-1.5) {\text{(1.05 g, 8.07 mmol), (S)-2-methyl-2-}};\node[below] at (0,-3) {\text{propanesulfinamide (1.03 g, 8.47 mmol) and Ti(OEt)$_4$ (7.36 g, 32.3 mmol) yielded 8S}};\node[below] at (0,-4.5) {\text{(1.50 g, 6.43 mmol, 80%) as a pale yellow oil. R$_f$ 0.6 (PE/EtOAc 50:50). [\alpha]_D^0 +248 (c \ 0.49, EtOH, 23 °C). \text{\textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 8.07 (d, $^3J_{HH}=4.1$ Hz, 1H), 4.85 (ddd, $^2J_{HH}=6.8$ Hz, $^3J_{HH}=5.1$ Hz, $^3J_{HH}=4.1$ Hz, 1H), 4.23 (dd, $^2J_{HH}=8.5$ Hz, $^3J_{HH}=6.8$ Hz, 1H), 4.05 (dd, $^2J_{HH}=8.5$ Hz, $^3J_{HH}=5.1$ Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.21 (s, 9H) ppm. \text{\textsuperscript{13}C NMR (75 MHz, CDCl$_3$) $\delta$ 168.0, 110.8, 76.9, 67.2, 57.0, 26.4, 25.4, 22.3 ppm. NMR spectra correspond to the reported data.}}\end{tikzpicture}}
\]

$(R,S,E)-N-[(2S)-2, 3-\text{cyclohexylenedioxy)propylidene}]2\text{-methyl-2-propanesulfinamide (9R)}$

\[
\text{\begin{tikzpicture}
\node[below] at (0,0) {\text{2,3-O, O-Cyclohexylidene-d-glyceraldehyde}};\node[below] at (0,-1.5) {\text{\textsuperscript{1}H NMR (400 MHz, CDCl$_3$) $\delta$ 8.03 (d, $^3J_{HH}=4.5$ Hz, 1H), 4.83 (ddd, $^2J_{HH}=7.2$ Hz, $^3J_{HH}=5.5$ Hz, $^3J_{HH}=4.5$ Hz, 1H), 4.24 (dd, $^2J_{HH}=8.6$ Hz, $^3J_{HH}=7.2$ Hz, 1H), 4.01 (dd, $^2J_{HH}=8.6$ Hz, $^3J_{HH}=5.5$ Hz, 1H), 1.77–1.53 (m, 8H), 1.48–1.34 (m, 2H), 1.21 (s, 9H) ppm. \text{\textsuperscript{13}C NMR (100 MHz, CDCl$_3$) $\delta$ 167.8, 111.6, 76.5, 66.8, 57.2, 36.0, 35.0, 25.0, 23.83, 23.80, 22.4 ppm. HRMS (MS+) for C$_{13}$H$_{23}$NNaO$_3$S (M+Na)$^+$ calcd 296.1291, found 296.1296.}}\end{tikzpicture}}
\]
(S,E)-N-[(2S)-2,3- Cyclohexyldenedioxo)propyldene]-2-methyl-2-propanesulfinamide (9S)

2,3- O,O-Cyclohexyldene-D-glyceraldehyde\(^{54}\) (1.0 g, 5.88 mmol), (S)-2-methyl-2-
propanesulfanilamide (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). \([\alpha]_D^\circ +193\) (c 0.53, EtOH, 22 °C). IR (neat) 2934 (m), 2359 (s), 1625 (m), 1364 (m), 1088 (s).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.07 (d, \(3J_{HH}=4.2\) Hz, 1H), 4.84 (ddd, \(3J_{HH}=6.7\) Hz, \(2J_{HH}=5.1\) 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\(_3\)) \(\delta\) 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\(_{23}\)N\(_2\)O\(_3\)S (M+Na)+
calcd 296.1291, found 296.1297.

(R,S)-N-[(2R,3R)-4-(Benzyloxy)-2,3-(cyclohexyldenedioxo)butyldene]-2-methyl-2-
propanesulfinamide (ent-10S)

SO\(_3\)•pyridine (3.27 g, 20.5 mmol, 3.0 equiv), Et\(_3\)N (3.34 mL, 23.9 mmol, 3.5 equiv),

DMSO (8 mL) and CH\(_2\)Cl\(_2\) (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\(_4\)Cl solution

and extraction with EtOAc (2 × 15 mL) and Et\(_2\)O (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\(_3\)) \(\delta\) 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–propanesulfaminamide (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 (s), 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, $^3J_{HH}=5.6$ 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$_4$S (M+Na)$_+$ calcd 416.1866, found 416.1873.

(S$_S$E)$-$N$-$[(2R,3R)$-$4$-$benzyloxy$-$2,3$-$(cyclohexylidenedioxy)$-$butylidene]$-$2$-$methyl$-$2$-$propanesulfaminamide (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–propanesulfaminamide (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 (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, $^3J_{HH}=5.6$ 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 167.2, 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$_4$S (M+Na)$_+$ calcd 416.1866, found 416.1873.
General procedure for the Honda-Reformatsky 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. I (3 equiv) was added immediately followed by dropwise addition of Et$_2$Zn (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$_4$Cl 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: (3R,Ss)-ethyl-3-(t-butylsulfinamino)-2,2-difluoropentanoate ul-11S (pale yellow oil): R$_f$ 0.20 (hexane/EtOAc 70:30). [α]$_D$ +62.9 (c 0.19, CHCl$_3$, 21 °C). IR (in CDCl$_3$) 3207 (br), 2982 (m), 1773(s), 1062 (s) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.32 (dq, $^2$J$_{HH}$=10.7, 3$^3$J$_{HH}$=7.2 Hz, 1H), 4.29 (dq, $^2$J$_{HH}$=10.7, 3$^3$J$_{HH}$=7.1 Hz, 1H), 3.81–3.66 (m, 1H), 3.15 (d, 3$^3$J$_{HH}$=8.9 Hz, 1H), 1.98–1.86 (m, 1H), 1.65–1.52 (m, 1H), 1.36 (t, 3$^3$J$_{HH}$=7.1 Hz, 3H), 1.20 (s, 9H), 1.14 (t, 3$^3$J$_{HH}$=7.4 Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 163.2 (t, $^2$J$_{CF}$=32.3 Hz), 114.8 (t, $^1$J$_{CF}$=255.7 Hz), 62.8, 60.8 (dd, $^2$J$_{CF}$=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 −119.1 (dd, $^2$J$_{FF}$=262.2 Hz, 3$^3$J$_{HF}$=17.2 Hz) ppm. MS (ESI+) (m/z) 349 (M+Na+MeCN)$^+$. HRMS (MS+) for C$_{11}$H$_{21}$F$_2$NNO$_2$O$_3$S (M + Na)$^+$ calcd 308.1102, found 308.1106.

Minor isomer: (3S,Ss)-ethyl-3-(t-butylsulfinamino)-2,2-difluoropentanoate l-11S (pale yellow oil): R$_f$ 0.23 (hexane/EtOAc 70:30). [α]$_D$ +26.6 (c 0.51, CHCl$_3$, 19 ºC). $^1$H NMR (400 MHz, CDCl$_3$) δ 4.39 (q, 3$^3$J$_{HH}$=7.1 Hz, 2H), 3.80–3.66 (m, 1H), 3.57 (d, 3$^3$J$_{HH}$=9.3 Hz, 1H),...
1.91–1.78 (m, 1H), 1.66–1.52 (m, 1H), 1.38 (t, $^{3}J_{HH}$=7.1 Hz, 3H), 1.24 (s, 9H), 1.06 (t, $^{3}J_{HH}$=7.4 Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_{3}$) δ 163.2 (t, $^{2}J_{CF}$=31.9 Hz), 114.7 (t, $^{1}J_{CF}$=256.4 Hz), 63.3, 60.4 (dd, $^{2}J_{CF}$=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, $^{2}J_{FF}$=264.3, $^{3}J_{HF}$=7.5 Hz), −118.4 (dd, $^{2}J_{FF}$=264.3 Hz, $^{3}J_{HF}$=15.6 Hz) ppm. MS (ESI+) (m/z) 308 (M+Na)$^+$. HRMS (MS+) for C$_{11}$H$_{21}$F$_{2}$NNaO$_{3}$S (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: (3R,S$_{2}$)-ethyl-3-(t-butylsulfinamino)-2,2-difluorotetradecanoate **ul-12S** (pale yellow oil):

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\text{C}_{11}\text{H}_{23}\text{CF}_{2}\text{COOEt} \quad R_{f} 0.19 \text{ (hexane/EtOAc 75:25). } [\alpha]_{D} +43.9 \text{ (c 0.54, CHCl}_{3}, 21 \degree\text{C}). IR (in CDCl}_{3} \\
\delta 4.33 (dq, ^{2}J_{HH}=10.9, ^{3}J_{HH}=7.2 \text{ Hz}, 1H), 4.29 (dq, ^{2}J_{HH}=10.9, ^{3}J_{HH}=7.2 \text{ Hz}, 1H), 3.79 (ddddd app. as ddtd, ^{3}J_{HH}=16.1, ^{3}J_{HH}=8.8, ^{3}J_{HH}=8.6, ^{3}J_{HH}=3.8 \text{ Hz}, 1H), 3.10 (d, ^{3}J_{HH}=8.8 \text{ Hz}, 1H), 1.87–1.76 (m, 1H), 1.73–1.59 (m, 1H), 1.59–1.22 (m, 18H), 1.36 (t, ^{3}J_{HH}=7.1 \text{ Hz}, 3H), 1.20 (s, 9H), 0.88 (t, ^{3}J_{HH}=7.0 \text{ Hz}, 3H) ppm. ^{13}C NMR (101 MHz, CDCl}_{3} \delta 163.3 (t, ^{2}J_{CF}=33.0 \text{ Hz}), 114.9 (t, ^{1}J_{CF}=255.4 \text{ Hz}), 62.9, 59.4 (dd, ^{2}J_{CF}=26.3 \text{ Hz}, ^{2}J_{CF}=23.4 \text{ 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} \delta −110.8 (dd, ^{2}J_{FF}=261.1 \text{ Hz}, ^{3}J_{HF}=8.6 \text{ Hz}), −118.8 (dd, ^{2}J_{FF}=261.1 \text{ Hz}, ^{3}J_{HF}=16.1 \text{ Hz}) ppm. MS (ESI+) (m/z) 475 (M+Na+MeCN)$^{+}. HRMS (MS+) for C$_{26}$H$_{39}$F$_{2}$NNaO$_{3}$S (M+Na)$^{+}$ calcd 434.2511, found 434.2516.
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Minor isomer: (3S,S$_{2}$)-ethyl-3-(t-butylsulfinamino)-2,2-difluorotetradecanoate **l-12S** (pale yellow oil): R$_{f}$ 0.17 (hexane/EtOAc 70:30). [α]$_{D}$ +61.9 (c 0.59, CHCl$_{3}$, 23 °C). $^{1}$H NMR (400 MHz, CDCl$_{3}$) δ 4.38 (q, $^{3}J_{HH}$=7.2 Hz, 2H), 3.86–3.72 (m, 1H), 3.56 (d, $^{3}J_{HH}$=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, $^{3}J_{HH}$=7.2 Hz, 3H), 1.23 (s, 9H), 0.89
(t, \( ^3J_{HH}=7.1\) Hz, 3H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) –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\(_2\)NNaO\(_3\)S (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 \(\rightarrow\) 65:35) afforded an inseparable mixture of diastereoisomers (68 mg, 0.180 mmol, 46%).

Analytically pure sample of the major diastereoisomer (3R,\(S\))-ethyl-4-(benzyloxy)-3-(\(tert\)-butylsulfinamino)-2,2-difluorobutanoate \textit{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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 162.9 (t, \( ^2J_{CF}=32.2\) Hz), 137.2, 128.4 (2C), 127.84, 127.79 (2C), 113.8 (t, \(J_{CF}=256.1\) 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\(_3\)) \(\delta\) –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\(_2\)NNaO\(_3\)S (M+Na)\(^+\) calcd 400.1365, found 400.1364.

Reaction with sulfinylimine \textit{ent-7S} (100 mg, 0.374 mmol) yielded \textit{ent-15S} (94:6 \(dr\)). Chromatography (PE/Et\(_2\)O 40:60 \(\rightarrow\) 20:80) afforded \textit{ent-ul-15S} (80 mg, 0.204 mmol, 54%) as a white solid and \textit{ent-l-15S} (4 mg, 0.010 mmol, 3%) as a pale yellow oil.
Major isomer: (3S,4S,R)-ethyl-4-(benzoxyl)-3-(t-butylsulfinamino)-2,2-difluropentanoate \textit{ent-ul-15S}: 

\[
\text{R', 0.10 (PE/Et}_2\text{O 40:60). Mp 109–111 °C. [\alpha]_{D}^0 -4.2 (c 0.14, CHCl}_3, 23 °C). IR (neat) 3213 (w, br), 2982 (w), 1771 (s), 1099 (s), 1054 (s). \text{H NMR (400 MHz, CDCl}_3) \delta 7.37–7.25 (m, 5H), 4.57 (d, \text{J}_{HH}=11.1 \text{ Hz, 1H}), 4.38 (d, \text{J}_{HH}=11.1 \text{ Hz, 1H}), 4.05–3.85 (m, 3H), 3.80 (dq as quin, \text{J}_{HH} 6.3=1 Hz, 1H), 3.71 (d, \text{J}_{HH}=9.5 \text{ Hz, 1H}), 1.44 (d, \text{J}_{HH}=6.3 \text{ Hz, 3H}), 1.24 (s, 9H), 1.16 (t, \text{J}_{HH}=7.1 \text{ Hz, 3H}) \text{ ppm.} \text{C NMR (101 MHz, CDCl}_3) \delta 163.0 (t, \text{J}_{CF}=32.2 \text{ Hz}), 137.4, 128.3 (2C), 128.2 (2C), 127.9, 114.2 (t, \text{J}_{CF}=254.7 \text{ Hz}), 74.9, 71.4, 63.3 (t, \text{J}_{CF}=23.4 \text{ Hz}), 62.6, 57.0, 22.5 (3C), 16.4, 13.7 ppm. \text{F NMR (282 MHz, CDCl}_3) \delta -110.0 (dd, \text{J}_{FF}=262.2 \text{ Hz, J}_{HF}=12.9 \text{ Hz}), -115.2 (dd, \text{J}_{FF}=262.2 \text{ Hz, J}_{HF}=12.9 \text{ Hz}). \text{MS (ESI+) (m/z) 414 (M+Na)+. HRMS (MS+) for C}_{18}H_{27}F_{2}NNaO_{4}S (M+Na)+ calcd 414.1521, found 414.1525.}
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Minor isomer: (3R,4S,R)-ethyl-4-(benzoxyl)-3-(t-butylsulfinamino)-2,2-difluropentanoate \textit{ent-l-15S}:

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\text{R, 0.20 (PE/Et}_2\text{O 40:60). [\alpha]_{D}^0 -33.5 (c 0.07, CHCl}_3, 23 °C). IR (neat) 2980 (w), 1770 (m), 1108 (s), 1082 (s), 1026 (s). \text{H NMR (400 MHz, CDCl}_3) \delta 7.38–7.25 (m, 5H), 4.56 (d, \text{J}_{HH}=11.1 \text{ Hz, 1H}), 4.36 (d, \text{J}_{HH}=11.1 \text{ Hz, 1H}), 4.31 (d, \text{J}_{HH}=10.5 \text{ Hz, 1H}), 4.09 (qd, \text{J}_{HH}=7.1 \text{ Hz, 2J}_{HH}=6.7 \text{ Hz, 1H}), 4.07 (qd, \text{J}_{HH}=7.1 \text{ Hz, 2J}_{HH}=6.7 \text{ Hz, 1H}), 4.00 (qt, \text{J}_{HH}=6.3 \text{ Hz, 3J}_{HH}=1.7 \text{ Hz, 1H}), 3.74 (dddd, \text{J}_{HH}=12.4 \text{ Hz, J}_{HH}=10.5 \text{ Hz, J}_{HH}=8.7 \text{ Hz, J}_{HH}=1.8 \text{ Hz, 1H}), 1.29 (d, \text{J}_{HH}=6.3 \text{ Hz, 3H}), 1.27 (s, 9H), 1.20 (t, \text{J}_{HH}=7.1 \text{ Hz, 3H}) \text{ ppm.} \text{C NMR (101 MHz, CDCl}_3) \delta 137.7, 128.3 (2C), 127.8 (3C), 113.6 (t, \text{J}_{CF}=257.6 \text{ Hz}), 72.1 (d, \text{J}_{CF}=2.9 \text{ Hz}), 71.1, 63.0 (t, \text{J}_{CF}=24.9 \text{ Hz}), 63.0, 57.2, 22.9 (3C), 16.6, 13.7 ppm (The C=O signal was not observed). \text{F NMR (282 MHz, CDCl}_3) \delta -108.0 (dd, \text{J}_{FF}=262.2 \text{ Hz, J}_{HF}=8.7 \text{ Hz}), -114.6 (dd, \text{J}_{FF}=262.2 \text{ Hz, J}_{HF}=8.7 \text{ Hz}). \text{MS (ESI) (m/z) 455 (M+Na+MeCN)+. HRMS (ESI) for C}_{18}H_{27}F_{2}NNaO_{4}S (M+Na)+ calcd 414.1521, found 414.1509.}
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Reaction with sulfinylimine ent-7R (100 mg, 0.374 mmol) yielded ent-15R (54:46 dr).

Chromatography (PE/Et₂O 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: (3R,4S,5S)-ethyl-4-(benzylxy)-3-(t-butylsulfinamino)-2,2-difluoropentanoate ent-ul-15R

(pale yellow oil): R, 0.38 (PE/Et₂O 20:80). [α]D +30.0 (c 0.62, CHCl₃, 23 °C). IR (neat) 3353 (w, br), 2979 (w), 1765 (m), 1079 (s), 1021 (s). ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.24 (m, 5H), 4.60 (d, ²JH-H=11.0 Hz, 1H), 4.33 (d, ³JH-H=11.0 Hz, 1H), 4.30 (d, ⁴JH-H=9.1 Hz, 1H), 4.09–3.98 (m, 3H), 3.66 (dddd, ³JH-H=12.8, ⁴JH-H=9.1 Hz, ⁵JH-H=8.9 Hz, ⁶JH-H=0.9 Hz, 1H), 1.42 (d, ⁶JH-H=6.4 Hz, 3H), 1.24 (s, 9H), 1.16 (t, ⁶JH-H=7.1 Hz, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 162.9 (dd, ²JCF=33.7, 30.7 Hz), 137.5, 128.3 (2C), 127.8 (2C), 127.7, 113.8 (t, ²JC=255.4 Hz), 70.7, 70.4 (d, ³JCF=2.9 Hz), 64.1 (dd, ²JC=27.8 Hz, ²JC=23.4 Hz), 62.7, 56.8, 22.5 (3C), 16.6, 13.7 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ –109.9 (dd, ²JHF=257.9 Hz, ³JHF=8.9 Hz), –114.7 (dd, ²JHF=257.9 Hz, ³JHF=12.8 Hz) ppm. MS (ESI+) (m/z) 414 (M+Na)⁺. HRMS (MS⁺) for C₁₈H₂₇F₂NNaO₄S (M+Na)⁺ calcd 414.1521, found 414.1526.

Minor isomer: (3S,4S,5S)-ethyl-4-(benzylxy)-3-(t-butylsulfinamino)-2,2-difluoropentanoate ent-l-15R

(pale yellow oil): R, 0.22 (PE/Et₂O 20:80). [α]D +37.7 (c 0.53, CHCl₃, 23 °C). IR (neat) 3213 (w, br), 2981 (w), 1770 (m), 1097 (s), 1055 (s). ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.24 (m, 5H), 4.51 (d, ²JH-H=11.2 Hz, 1H), 4.39 (d, ³JH-H=11.2 Hz, 1H), 4.08–3.92 (m, 3H), 3.76–3.68 (m, 1H), 3.68 (d, ³JH-H=9.3 Hz, 1H), 1.32 (d, ³JH-H=6.1 Hz, 3H), 1.24 (s, 9H), 1.18 (t, ³JH-H=7.1 Hz, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 137.4, 128.3 (2C), 128.0 (2C), 127.8, 113.8 (t, ²JC=254.7 Hz), 73.9, 71.0, 62.8, 62.7 (dd, ²JC=23.4 Hz, ²JC=22.0 Hz), 57.1, 22.7 (3C), 16.6, 13.7 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ –109.6 (dd, ²JHF=262.2 Hz, ³JHF=8.6 Hz), –117.3 (dd, ²JHF=262.2 Hz, ³JHF=17.2 Hz) ppm. MS (ESI) (m/z) 455 (M+Na+MeCN)⁺. HRMS (MS⁺) for C₁₈H₂₇F₂NNaO₄S (M+Na)⁺ calcd 414.1521, found 414.1524.
Reaction with sulfinylimine 8S (109 mg, 0.467 mmol) yielded 16S as a single diastereoisomer.

Chromatography (PE/EtOAc 70:30→50:50) afforded 16S (103 mg, 0.288 mmol, 62%) as a white solid.

Major isomer: (3R,4S,S)-ethyl-4,5-isopropylidenedioxy-3-(t-butylsulfiny lamino)-2,2-

difluoropentanoate 16S: Rf 0.26 (PE/EtOAc 50:50). Mp 88–90 °C. [α]D +30.3 (c 0.29, CHCl3, 23 °C). IR (neat) 3194 (w), 2986 (w), 1777 (m), 1761 (m), 1053 (s). 1H NMR (300 MHz, CDCl3) δ 4.38–4.11 (m, 5H), 3.96 (dddd, 3JHF=17.4 Hz, 3JHH=8.7 Hz, 3JHF=8.2 Hz, 3JHH=7.2 Hz, 1H), 1.39 (s, 3H), 1.34 (t, 3JHH=7.2 Hz, 3H), 1.29 (s, 3H), 1.21 (s, 9H) ppm. 13C NMR (75 MHz, CDCl3) δ 162.9 (t, 2JCF=30.8 Hz), 113.8 (dd, 1JCF=256.4 Hz, 1JCF=252.5 Hz), 110.6, 73.6, 66.8, 63.0, 61.1 (dd, 2JCF=22.6 Hz, 2JCF=21.5 Hz), 57.1, 25.9, 24.9, 22.4 (3C), 13.7 ppm. 19F NMR (282 MHz, CDCl3) δ –110.0 (dd, 2JFF=262.6 Hz, 3JHF=8.2 Hz), –119.4 (dd, 2JFF=262.6 Hz, 3JHF=17.4 Hz) ppm. MS (ESI+) (m/z) 421 (M+Na+MeCN)+. HRMS (MS+) for C14H25F2NNaO5S (M+Na) calcld 380.1314, found 380.1312.

Minor isomer: (3S,4S,S)-ethyl-4,5-isopropylidenedioxy-3-(t-butylsulfiny lamino)-2,2-

difluoropentanoate 16S (isolated from an unselective reaction, pale yellow oil): [α]D +6.2 (c 0.17, CHCl3, 23 °C). IR (neat) 2991 (w), 1770 (s), 1137 (s), 1123 (s), 1107 (s) ppm. 1H NMR (300 MHz, CDCl3) δ 4.51 (ddd, 3JHH=7.1 Hz, 3JHH=6.1 Hz, 3JHH=2.2 Hz, 1H), 4.45–4.32 (m, 2H), 4.11 (dd, 2JHH=8.2 Hz, 3JHH=7.1 Hz, 1H), 4.14 (d, 3JHH=10.4 Hz, 1H), 3.85 (ddd, 3JHH=16.3 Hz, 3JHH=10.4 Hz, 3JHH=6.1 Hz, 3JHH=2.2 Hz, 1H), 3.80 (dd, 2JHH=8.2 Hz, 3JHH=6.1 Hz, 1H), 4.44 (s, 3H), 1.38 (t, 3JHH=7.2 Hz, 3H), 1.33 (s, 3H), 1.26 (s, 9H) ppm. 13C NMR (75 MHz, CDCl3) δ 162.7 (t, 2JCF=31.4 Hz), 113.5 (dd, 1JCF=261 Hz, 1JCF=256 Hz), 110.2, 72.1 (d, 3JCF=3.3 Hz), 66.1, 63.5, 59.4 (t, 2JCF=24.8 Hz), 57.3, 26.1, 24.4, 22.6 (3C), 13.7 ppm. 19F NMR (282 MHz, CDCl3) δ –107.0 (dd,
$^2J_{HF}$=265.7 Hz, $^3J_{HH}$=6.1 Hz), -117.9 (dd, $^2J_{FF}$=265.7 Hz, $^3J_{HH}$=16.3 Hz) ppm. HRMS (MS+) for C$_{14}$H$_{23}$F$_2$NNaO$_5$S (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: (3S,4S,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. [α]$_D$ –62.5

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, $^2J_{HF}$=262.2 Hz, $^3J_{HF}$=8.6 Hz), –118.1 (dd, $^2J_{HF}$=262.2 Hz, $^3J_{HF}$=17.2 Hz) ppm. MS (ESI+) (m/z) 421

((M+Na+MeCN)$^+$). HRMS (MS+) for C$_{14}$H$_{23}$F$_2$NNaO$_5$S (M+H)$^+$ calcd 358.1500, found 358.1494.

Minor isomer: (3R,4S,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 . [α]$_D$ –

22.6 (c 0.06, CHCl$_3$, 22 °C). IR (neat) 3205 (br w), 2986 (br m), 1775 (s), 1065 (s)

ppm. $^1$H 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, $^2J_{HF}$=262.2 Hz, $^3J_{HF}$=
HRMS (MS+) for C_{14}H_{26}F_{2}NO_{5}S (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%).

(3R,4S,5S)-Ethyl-4,5-cyclohexyldenedioxy-3-(t-butylsulfinylamino)-2,2-difluoropentanoate ul-17S (white solid): R<sub>f</sub> 0.23 (PE 40-60 °C/EtOAc 50:50). Mp 112–116 °C. [α]<sub>D</sub> +28.3 (c 0.56, CHCl<sub>3</sub>, 23 °C). IR (neat) 3203 (br, w), 2937 (m), 1761 (m), 1092 (m), 1050 (s). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.37–4.06 (m, 5H), 3.96 (dddd, <sup>3</sup>J<sub>HF</sub>=17.2 Hz, <sup>3</sup>J<sub>HF</sub>=8.6 Hz, <sup>3</sup>J<sub>HH</sub>=8.5 Hz, <sup>3</sup>J<sub>HH</sub>=7.3 Hz, 1H), 3.54 (d, <sup>3</sup>J<sub>HH</sub>=8.5 Hz, 1H), 1.70–1.45 (m, 8H), 1.44–1.28 (m, 2H), 1.35 (t, <sup>3</sup>J<sub>HH</sub>=7.1 Hz, 3H), 1.21 (s, 9H) ppm. 13C NMR (101 MHz, CDCl<sub>3</sub>) δ 162.8 (t, <sup>2</sup>J<sub>CF</sub>=30.7 Hz), 113.9 (dd, <sup>1</sup>J<sub>CF</sub>=256.1 Hz, <sup>1</sup>J<sub>CF</sub>=251.8 Hz), 111.3, 73.2, 66.5, 62.9, 61.1 (t, <sup>2</sup>J<sub>CF</sub>=22.0 Hz), 57.1, 35.6, 34.2, 24.9, 23.8, 23.6, 22.4 (3C), 13.8 ppm. 19F NMR (282 MHz, CDCl<sub>3</sub>) δ −109.5 (dd, <sup>2</sup>J<sub>FF</sub>=264.3 Hz, <sup>3</sup>J<sub>HF</sub>=8.6 Hz), −118.9 (dd, <sup>2</sup>J<sub>FF</sub>=264.3 Hz, <sup>3</sup>J<sub>HF</sub>=17.2 Hz) ppm. MS (ESI+) (m/z) 421 (M+Na+MeCN)<sup>+</sup>. HRMS (MS+) for C<sub>14</sub>H<sub>26</sub>F<sub>2</sub>NO<sub>5</sub>S (M+H)<sup>+</sup> calcd 398.1807, found 398.1804.

Reaction with sulfinylimine 9R (100 mg, 0.366 mmol) yielded 17R (81:19 <i>dr</i>). 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: (3S,4S,R)<sub>s</sub>-ethyl-4,5-cyclohexyldenedioxy-3-(t-butylsulfinylamino)-2,2-difluoropentanoate ul-17R: R<sub>f</sub> 0.21 (PE/EtOAc 65:35). Mp 72–75 °C. [α]<sub>D</sub> −29.9 (c 0.68, CHCl<sub>3</sub>, 21 °C). IR (neat) 3311 (br w), 2935 (m), 1770 (s), 1075 (s) cm<sup>−1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.43 (t, <sup>3</sup>J<sub>HH</sub>=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, <sup>3</sup>J<sub>HH</sub>=7.2 Hz, 3H), 1.25 (s, 9H) ppm. 13C NMR (101 MHz, CDCl<sub>3</sub>) δ 162.7 (t, <sup>2</sup>J<sub>CF</sub>=30.7 Hz), 113.9 (t, <sup>1</sup>J<sub>CF</sub>=259.1 Hz), 111.0, 70.5
Reaction with sulfinylimine ent-10R (2.06 g, 5.24 mmol) yielded ent-ul-18R (single diastereoisomer). Chromatography (PE/EtOAc 75:25→60:40) afforded ent-ul-18S (1.81 g, 3.50 mmol, 67%).

 Minor isomer: (3R,4S,R,S)-ethyl-4,5-cyclohexyldenedioxy-3-(t-butylsulfinylamino)-2,2-
difluoropentanate I-17R: R, 0.12 (PE/EtOAc 65:35). Mp 122–124 °C [α]D −39.0 (c 0.50, CHCl₃, 19 °C). IR (neat) 3204 (br w), 2937 (m), 1762 (s), 1053 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 4.36 (dq, J₁HH=10.7, J₂HH=7.2 Hz, 1H), 4.30 (dq, J₁HH=10.7, J₂HH=7.2 Hz, 1H), 4.25–4.18 (m, 1H), 4.15–4.08 (m, 1H), 3.98 (ddddd app. ddt, J₂HH=16.1, J₁HH=9.1, J₃HH=8.6 Hz, 1H), 3.83 (dd, J₁HH=8.6, 6.3 Hz, 1H), 3.67 (d, J₁HH=9.1 Hz, 1H), 1.63–1.48 (m, 8H), 1.43–1.31 (m, 2H), 1.36 (t, J₁HH=7.2 Hz, 3H), 1.23 (s, 9H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 162.6 (t, JCF=30.7 Hz), 113.7 (dd, J₁CF=256.1 Hz, J₂CF=253.2 Hz), 111.2, 73.2 (br. s), 66.8, 63.2, 61.1 (t, J₁CF=22.0 Hz), 57.1, 35.8, 34.4, 24.9, 23.8, 23.6, 22.6 (3C), 13.8 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ −108.6 (dd, J₁FF=262.8, J₂FF=8.6 Hz), −118.3 (d, J₁FF=262.2, J₂FF=16.1 Hz) ppm. MS (ESI+) (m/z) 461 (M+Na+MeCN)⁺ HRMS (MS⁺) for C₁₇H₂₄F₂NO₅S (M+H)⁺ calcd 398.1807, found 398.1808.

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%).

(3S,4R,S,R,S)-Ethyl-[6-(benzyloxy)-3-(t-butylsulfinylamino)-4,5-cyclohexyldenedioxy)-2,2-
difluorohexanoate ent-ul-18S (pale yellow oil): R, 0.35 (PE/EtOAc 50:50). [α]D +43.2 (c 0.35, CHCl₃, 22 °C). IR (neat) 3244 (w), 2936 (m), 2360 (m), 1774 (m), 1759 (m), 1060 (s). ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.27 (m, 5H), 4.62 (d, J₁HH=6.4 Hz, 1H), 4.56 (s, 2H), 4.49 (dd, J₁HH=8.8 Hz, J₂HH=6.8 Hz, J₃HH=4.4 Hz, 1H), 4.32 (dq, J₁HH=10.7 Hz, J₂HH=7.1 Hz, 1H), 4.28 (dq, J₁HH=10.7 Hz, J₂HH=7.1 Hz, 1H), 4.13 (dd, J₃HH=8.5 Hz,
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: (3R,4R,5R,S)-ethyl-6-(benzoxo)3-((t-buty)sulfinylamino)-4,5- 
(cyclohexylenedioxy)-2,2-difluorohexanoate **ent-ul-18R** (pale yellow oil): \( R_f \), 0.37 (PE/EtOAc 70:30). \( [\alpha]_D \) +50.8 (c 0.53, CHCl₃, 20 °C). IR (neat) 2936 (s), 2863 (w), 1773 (m), 1760 (m), 1073 (s). \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.40–7.24 (m, 5H), 4.63 (d, \(^3\)J\(_{HH}\)=12.1 Hz, 1H), 4.59 (d, \(^3\)J\(_{HH}\)=12.1 Hz, 1H), 4.51–4.44 (m, 2H), 4.30 (dq, \(^3\)J\(_{HH}\)=10.7 Hz, \(^3\)J\(_{HH}\)=7.2 Hz, 1H), 4.26 (dq, \(^3\)J\(_{HH}\)=10.7 Hz, \(^3\)J\(_{HH}\)=7.2 Hz, 1H), 4.20 (d, \(^3\)J\(_{HH}\)=8.7 Hz, 1H), 4.05 (ddd, \(^3\)J\(_{HH}\)=17.2 Hz, \(^3\)J\(_{HH}\)=8.7 Hz, \(^3\)J\(_{HH}\)=7.5 Hz, 1H), 3.78 (dd, \(^3\)J\(_{HH}\)=10.1 Hz, \(^3\)J\(_{HH}\)=4.2 Hz, 1H), 3.62 (dd, \(^3\)J\(_{HH}\)=10.1 Hz, \(^3\)J\(_{HH}\)=6.4 Hz, 1H), 1.77–1.47 (m, 8H), 1.44–1.30 (m, 2H), 1.33 (t, \(^3\)J\(_{HH}\)=7.2 Hz, 3H), 1.24 (s, 9H) ppm. \(^1\)C NMR (101 MHz, CDCl₃) \( \delta \) 162.8 (t, \(^3\)J\(_{CF}\)=33.7 Hz), 137.9, 128.3 (2C), 127.6 (3C), 114.0 (dd, \(^1\)J\(_{CF}\)=259.1 Hz, \(^1\)J\(_{CF}\)=254.7 Hz), 110.8, 74.3, 74.2 (d, \(^3\)J\(_{CF}\)=2.9 Hz), 73.6, 69.5, 62.9, 57.7 (t, \(^3\)J\(_{CF}\)=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, CDCl₃) \( \delta \) −109.1 (dd, \(^3\)J\(_{FF}\)=257.9 Hz, \(^3\)J\(_{HF}\)=7.5 Hz), −117.9 (dd, \(^3\)J\(_{FF}\)=257.9 Hz, \(^3\)J\(_{HF}\)=10.1 Hz), 1.30 (m, 2H), 1.30 (m, 2H), 1.61–1.45 (m, 7H), 1.36 (t, \(^3\)J\(_{HH}\)=7.1 Hz, 3H), 1.44–1.26 (m, 2H), 1.08 (s, 9H) ppm. \(^13\)C NMR (101 MHz, CDCl₃) \( \delta \) 163.1 (t, \(^3\)J\(_{CF}\)=30.7 Hz), 136.9, 128.6 (2C), 128.1 (3C), 114.0 (dd, \(^1\)J\(_{CF}\)=257.6 Hz, \(^1\)J\(_{CF}\)=251.8 Hz), 111.6, 76.5, 76.2, 73.9, 71.1, 62.8, 61.7 (t, \(^3\)J\(_{CF}\)=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, CDCl₃) \( \delta \) −110.8 (dd, \(^3\)J\(_{FF}\)=260.0 Hz, \(^3\)J\(_{HF}\)=7.5 Hz), −121.4 (dd, \(^3\)J\(_{FF}\)=260.0 Hz, \(^3\)J\(_{HF}\)=17.2 Hz) ppm. MS (ESI+) (m/z) 540 (M+Na)\(^+\). HRMS (MS+) for C\(_{25}\)H\(_{38}\)F\(_2\)NO\(_6\)S (M+H)\(^+\) calcd 518.2382, found 518.2377.
$^3J_{HH}=17.2$ Hz) ppm. MS (ESI+) ($m/z$) 540 (M+Na$^+$). HRMS (MS+) for $C_{25}H_{38}F_2NO_6S$ (M+H)$^+$ calc 518.2382, found 518.2378.

Minor isomer: (3$S$,4$R$,5$R$,6$S$)-ethyl-6-(benzyloxy)-3-(t-butsulfinylamino)-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$_3$) $\delta$ 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, $^1J_{HH}=9.2$ 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$_3$) $\delta$ 162.8 (t, $^2J_{CF}=31.1$ Hz), 137.6, 128.5 (2C), 128.0 (2C), 127.9, 113.8 (dd, $^1J_{CT}=256.5$ Hz, $^1J_{CT}=255.0$ Hz), 111.4, 77.5, 76.0 (t, $^3J_{CT}=2.6$ Hz), 73.7, 71.1, 63.2, 60.7 (t, $^2J_{CT}=22.7$ 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$_3$) $\delta$ –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$^+$) calc 540.2202, found 540.2192.

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**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/](http://pubs.acs.org/).

**References**

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