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Convenient Asymmetric Synthesis of β-Substituted α,α-Difluoro-β-amino Acids via Reformatsky Reaction between Davis' *N*-Sulfinylimines and Ethyl Bromodifluoroacetate

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The enantiopure Davis' *N*-sulfinylimines were found to be efficient as chiral imine equivalents in the high-temperature Reformatsky-type additions with $BrZnCF_2COOEt$ affording an efficient approach to the enantiomerically pure α,α-difluoro-β-amino acids. High chemical and stereochemical yields (drs > 9:1, and as high as 99:1) render this method immediately useful for preparing the target amino acids.

Introduction

The recent decade has witnessed a series of fascinating discoveries in the area of nonnatural foldamers, the sequence-specific oligomers that mimic various aspects of the folding, organization, and function of biological polymers.[1] In particular, increasing work has been devoted to the study of β-peptides,[2] the nonbiological polymers most closely resembling conventional, natural α-peptides. In the recent years a large body of synthetic work on β-peptides has laid a solid foundation for rational design of these nonnatural polymers with exciting potential practical applications in the areas of pharmaceuticals and material science.[1−3] Considering the exciting benefits of fluorine substitution for hydrogen established in the series of α-amino acids and α-peptides, such as rational modification of lipophilicity/hydrophobicity, chemical reactivity and modification of the peptides secondary structures,[4] synthesis, and systematic study of fluorinated β-amino acids and β-peptides might be of particular interest. However, to the best of our knowledge, fluorine-containing β-peptides have not been reported thus far.[1−3] Therefore, we set for ourselves a goal to design and synthesize fluorinated β-peptides for a systematic study of their physicochemical and biological properties. We envisioned two strategically different approaches for fluorine substitution for hydrogen in β-peptides: the fluorinated inside and fluorinated outside surfaces of a folded peptide. The β-peptides with fluorinated outside surface could be designed by using β-amino acids of type **1** (Figure 1), where the trifluoromethyl group can be generally substituted with a perfluoroalkyl or perfluoroaryl moiety. Another type of fluorinated β-peptides with the fluorinated inside surface of a folded peptide can be realized with an application of α,α-difluoro-β-amino acids **2**, where substituent R could be rationally introduced to control lipophilicity/hydrophobicity, acid/base properties, as well as the desired 3D structure of the target β-peptide. To take on these interesting targets, we needed convenient and reliable asymmetric methods for preparing amino acids **1** and **2** in enantiomerically pure form and on a relatively large scale. Recently we[5] and others[6] have developed several methodologically different and

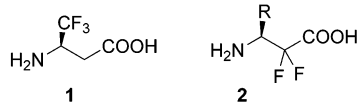

FIGURE 1. Two different strategies for fluorine substitution for hydrogen in β-peptides.

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(4) (a) *Fluorine-Containing Amino Acids. Synthesis and properties*; Kukhar', V. P., Soloshonok, V. A., Eds.; John Wiley and Sons Ltd.: Chichester, UK, 1994. (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Books, American Chemical Society: Washington, DC, 1996. (c) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: Chichester, UK, 1999.

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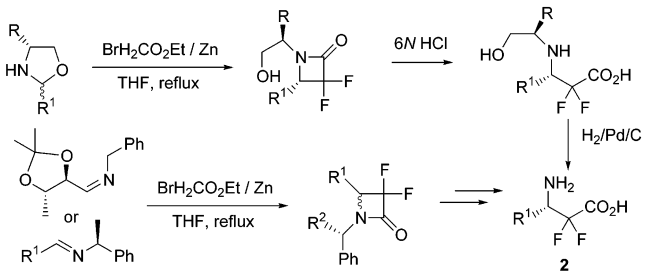
generalized approaches to enantiomerically pure β-fluoroalkyl-β-amino acids of type **1**. In particular, the biomimetic approach developed by us for reductive amination of fluorocarbonyl compounds into the corresponding amines and amino acids, in its asymmetric version,[7] enjoys key advantages of a truly practical methodology such as attractive cost structure and operationally convenient conditions.

On the other hand, despite the considerable interests in enantiomerically pure α,α-difluoro-β-amino acids of type **2**, as precursors to a particular type of fluorinated β-lactam antibiotics,[8] only two,[9] to the best of our knowledge,[10,11] reports in the literature deal with the asymmetric synthesis of β-amino acids **2**. In the earlier report[9a] the authors studied Reformatsky addition between in situ generated $XZnCF_2COOR$ (X = halogen) and *N*-benzylimine of (*R*)-glyceraldehyde acetonide and a series of aromatic aldimines derived from (*S*)- or (*R*)-α-methylbenzylamine (Scheme 1). In both cases the stereochemical outcome was found to be disappointingly low (de < 50%). In a recent paper[9b] the authors reported a similar Reformatsky-type reaction using chiral 1,3-oxazolidines as stable equivalents of the required imines (Scheme 1). The reactions were shown to proceed with high diastereoselectivity furnishing the corresponding azetidin-2-ones with up to 99% de. However, the chemical yields were much less satisfactory, ranging from 32 to 69%. Furthermore, the additional 2−3 steps required for transformation of the azetidin-2-ones to the target α,α-difluoro-β-amino acids **2** led to low overall yields rendering this approach synthetically problematic. Here we report a full account[12] of our studies on the application of the Davis' chiral sulfinimines in the addition reaction with the in situ generated $BrZnCF_2COOEt$ (**3**), as a generalized method for preparing enantiomerically pure α,α-difluoro-β-amino acids **2**. Our results demonstrate that this method offers a superior synthetic alternative to the previous approaches,[9,10] featuring high chemical and stereochemical outcome, as well as simple experimental conditions. Furthermore, the results obtained suggest that application of readily available and inexpensive *p*-toluenesulfinimines[14] in the reactions with ethyl bromodifluoroacetate affords the target β-amino acids **2** with higher stereochemical outcome as compared with the data reported recently[11,13] on the additions of the corresponding *tert*-butylsulfinimines[15] with the reagent **3**.

SCHEME 1



Results and Discussion

Among a vast variety of synthetic approaches reported for asymmetric preparation of β-amino acids,[16] our attention was attracted by the method developed by Davis and co-workers.[14] The key step of their protocol consists of the highly diastereoselective Reformatsky-type addition of the metal enolate of methyl acetate to the enantiopure *p*-toluenesulfinimines **4** at −78 °C. Hydrolysis of the corresponding addition products under mild conditions affords the target β-amino acids in high overall chemical yields. The application of the *N*-sulfinyl group as a chiral auxiliary was shown to possess several synthetically important advantages over other imine auxiliaries: (i) It is relatively cheap and readily available,[17] (ii) increases electrophilicity of the C,N double bond, (iii) is highly stereocontrolling, and (iv) is easily removed under mild acidic conditions without any extent of epimerization.[14] On the other hand, the possibility of application of enantiopure *p*-toluenesulfinimines **4** in the

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(10) (a) Separation of racemic derivatives by preparative chiral HPLC: Uoto, K.; Ohsuki, S.; Takenoshita, H.; Ishiyama, T.; Iimura, S.; Hirota, Y.; Mitsui, I.; Terasawa, H.; Soga, T. *Chem. Pharm. Bull.* **1997**, *45*, 1793. (b) Conversion of enantiomerically enriched β,β-difluoro-β-hydroxy derivatives to the corresponding β-amino acids via Mitsunobu protocol: Iseki, K.; Yoshichika, K.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271. (c) Diastereomers separation: Nakayama, K.; Kawato, H. C.; Inagaki, H.; Nakajima, R.; Kitamura, A.; Someya, K.; Ohta, T. *Org. Lett.* **2000**, *2*, 977−980. (d) Solid-phase synthesis of *N*-substituted derivatives: Vidal, A.; Nefzi, A.; Houghten, R. A. *J. Org. Chem.* **2001**, *66*, 8268.

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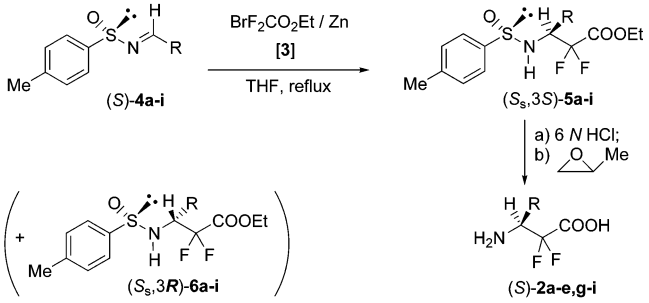
SCHEME 2



R = C_6H_5 (**a**), 4-MeO-C_6H_4 (**b**), 4-F-C_6H_4 (**c**), 4-Cl-C_6H_4 (**d**), 4-CF_3-C_6H_4 (**e**), 2-furyl (**f**), *n*-C_5H_{11} (**g**), *i*-Pr (**h**), *t*-Bu (**i**)

addition reactions with $BrZnCF_2COOEt$ (**3**) raised several serious concerns regarding the stereochemical outcome of the reactions. First, it was shown that the nature of the metal (Li^+, Na^+) enolate of methyl acetate in the reaction with *N*-benzylidene-*p*-toluenesulfinimine (**4a**) had a dramatic effect on the diastereoselectivity of the addition;[14c] therefore, the effect of Zn^{2+} cannot be predicted. Second, since it was demonstrated that the fluorinated Reformatsky reagents of type **3** (Scheme 2) predominantly exist and react in the carbon−zinc form,[18] one may expect a profound difference in the corresponding transition states between the reactions of the enantiopure *p*-toluenesulfinimines **4** with the Reformatsky regent **3** and the predominantly metal−oxygen coordinated enolates of methyl acetate.[19] Furthermore, very high diastereoselectivity (>98%) of the addition between the *p*-toluenesulfinimine **4** and the sodium enolate of methyl acetate was obtained for the reaction conducted in diethyl ether at −78 °C.[14c] Therefore, taking into consideration that the fluorinated Reformatsky reagent $BrZnCF_2COOR$ is usually generated[18,20] and reacted, due to its instability,[20,21] in a refluxing THF,[22] one may anticipate lower diastereoselectivity of its additions to *p*-toluenesulfinimines **4** as compared with that of the literature low-temperature reactions.[14,17,23]

Despite all these rather discouraging considerations, we were still interested in studying the addition reactions of the fluorinated Reformatsky reagent **3** to the enantiopure *p*-toluenesulfinimines **4**. First we conducted the reaction between **3** and (*S*)-*N*-benzylidene-*p*-toluenesulfinimine (**4a**) (Scheme 2). The reaction of sulfinimine **4a** with ethyl bromodifluoroacetate conducted in the presence of activated Zn powder in boiling THF was completed in 15 min furnishing the corresponding *p*-toluenesulfinamide **5a** as a sole reaction product. In a series of experiments designed to optimize the chemical yield of addition product **5a**, we found that a 1:2 ratio of sulfinimine **4a** and $BrCF_2COOEt$ was required for complete transformation of the former to sulfinamide **5a**, isolated with over 80% yield (Table 1, entry 1). Diastereoselectivity of the addition, determined by NMR (^{19}F, ^1H) on crude reaction mixture, was found to be surprisingly high. Considering the above-mentioned concerns, in particular, the high temperature of the addition, a 96/4 ratio of the diastereomers (Table 1, entry 1) was remarkable. Crystallization of the crude mixture from hexane/ethyl acetate afforded the major diastereomer in optically pure form. To determine the absolute configuration of the newly formed stereogenic carbon in the major product **5a**, it was hydrolyzed to the target free amino acid **2a** (Scheme 2). Enantiomeric purity (>99% ee) of the obtained amino acid **2a** was confirmed by HPLC analysis on chiral sorbents.[24] Comparison of the sign and magnitude of an optical rotation obtained for **2a** with the literature data[9b] revealed its (*S*) absolute configuration, therefore stereochemistry of the addition product **5a** was assigned to be (S_s,3*S*). Application of the (*R*)-configured starting sulfinimine **4a** in the reaction with **3** mirrored the results obtained for (*S*)-**4a**, giving rise to (R_s,3*R*)-**5a** in 92% de (entry 2). Next we studied the generality of the reaction using aromatic sulfinimines **4b**−**f** bearing electron-releasing and electron-withdrawing substituents; all reactions were conducted under the standard

TABLE 1. Reformatsky Reactions between in Situ Generated Reagent 3 and Davis' *N*-*p*-tOluenesulfinimines (*S*)-4a−i[a]

		products **5**			products **2**
entry	**4a**−**i**	yield,[b] %	de,[c] %	config[d]	yield,[e] %
1	**a**	82	92	(S_s,3*S*)	88
2	**a**	84	92	(R_s,3*R*)[f]	
3	**b**	82	>98	(S_s,3*S*)	96
4	**c**	83	94	(S_s,3*S*)	82
5	**d**	85	93	(S_s,3*S*)	78
6	**e**	85	80	(S_s,3*S*)	94
7	**f**	77	86	(S_s,3*S*)	*g*
8	**g**	59 (8)[h]	72	(S_s,3*S*)	56
9	**h**	65 (11)[i]	72	(S_s,3*S*)	63
10	**i**	60	76	(S_s,3*S*)	70

[a] All reactions were conducted by slow addition of a solution of 2 equiv of ethyl bromodifluoroacetate and 1 equiv of imine **4a**−**i** in THF to a refluxing suspension of 2 equiv of activated Zn powder in THF. [b] Isolated yields of pure products after column chromatography. [c] Determined by ^{19}F and ^1H NMR analysis of the crude reaction mixtures. [d] Determined by comparison of the sign and magnitude of the optical rotation compared with the literature data; see also the text. [e] Isolated yields of pure products. [f] (*R*)-Configured imine **4a** was used. [g] Attempts to hydrolyze **5f** to afford the corresponding free acid **2f** failed. [h] Minor product (S_s,3*R*)-**6g** was isolate in 8% chemical yield. [i] Minor product (S_s,3*R*)-**6h** was isolate in 11% chemical yield.

(17) For the recent, improved synthesis of the *N*-*p*-toluenesulfinimines, see: (a) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zang, H. *J. Org. Chem.* **1999**, *64*, 1403. (b) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carrol, P. S. *J. Org. Chem.* **1997**, *62*, 2555−2563. (c) Davis, F.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559−7567.

(18) Barton and co-workers demonstrated that the α,α-difluoro-Reformatsky reagents generated in ether-type solvents exist in carbon−metal form, see: Barton, D.; Easdon, J. *J. Fluorine Chem.* **1988**, *38*, 125.

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(21) Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 1803.

(22) The Reformatsky reagent $IZnCF_2COOMe$ could be generated at room temperature by treating a methyl iododifluoroacetate with activated Zn powder; see ref 9a.

(23) Besides the high temperature, as an unfavorable factor for achieving high diastereoselectivity in the addition reactions under study, the use of THF as a solvent was shown to result in reduced stereoselectivity as compared with the stereochemical outcome of the reactions conducted in diethyl ether; see refs 14c and 19.

(24) The procedures previously developed for determination of enantiomeric composition of various β-amino acids were used: Galushko, S. V.; Shishkina, I. P.; Soloshonok, V. A. *J. Chromatogr.* **1992**, *592*, 345. Racemic samples of amino acids **2a**−**e**,**g**−**i** were prepared by the method described in this paper protocol, using racemic **4a**−**e**,**g**−**i** as starting compounds.

conditions. The addition of *p*-methoxy-containing (*S*)-**4b** afforded the product **5b** with unexpectedly improved diastereoselectivity (entry 3). Thus, only one diastereomeric product (S_s,3*S*)-**5b** was detected in the crude reaction mixture. On the other hand, the reactions of *p*-fluoro- and *p*-chloro-substituted (*S*)-**4c**,**d** gave rise to the diastereomeric products **5c**,**d** with the stereochemical outcome comparable with that observed in the addition of unsubstituted *N*-benzylidene derivative **4a** (entries 1,2 vs 4,5). In contrast, the additions of *p*-trifluoromethyl- and 2-furyl-conaining sulfinimines **4e**,**f** proceeded with lower stereochemical outcome as compared with the diastereoselectivity observed in the reactions of *N*-benzylidene derivative **4a** (entries 1,2 vs 6,7). Nevertheless, the diastereomerically pure derivatives **5e** and **5f** were isolated in synthetically useful chemical yields by recrystallization of the crude reaction mixtures.

Taking advantage of the high crystallinity of the *p*-trifluoromethyl-containing **5e** we performed its X-ray analysis, which confirmed the expected (S_s,3*S*) absolute configuration of **5e**. It is necessary to note that the diastereomers (S_s,3*S*)-**5** and (S_s,3*R*)-**6** showed very close R_f values in most of the commonly used solvents, posing the problem of their separation by column chromatography. On the other hand, we found that isolation of the major products (S_s,3*S*)-**5** can be efficiently achieved by a single crystallization of the mixture from hexane/ethyl acetate. Hydrolysis of diastereomerically pure sulfinamides **5a**−**e** was readily accomplished by refluxing with 6 N HCl to afford, after treatment with propylene oxide, the target α,α-difluoro-β-amino acids **2a**−**f** in high isolated yield. The hydrolysis was typically carried out for 4 h to ensure complete removal of the sulfinamide as well as ester moieties. Enantiomeric purity of thus obtained amino acids **2a**−**e** was shown by the chiral HPLC analysis[24] to be greater than 99% ee. The only exception was the hydrolysis of furyl-substituted product **5f**. In this case we failed to isolate the target amino acid **2f** using the standard procedure, probably due to instability of the furyl ring under the relatively strong acidic conditions.

Considering the data obtained, we can suggest that the high-temperature Reformatsky addition reactions between aromatic sulfinimines **4a**−**e** and in situ generated **3** could be regarded as a generalized and synthetically useful approach to the target β-aryl-substituted β-amino acids **2**. Since the high diastereoselectivity in these high-temperature addition reactions was rather unexpected, we assumed that the presence of the fluorine atoms in reagent **3** might have some effect on the stereochemical outcome.[25] Therefore, we decided to conduct the reaction between sulfinimines **4a** and fluorine-free ethyl bromoacetate using our standard reaction conditions (Scheme 3). Surprisingly, the reaction of **4a** with in situ generated Reformatsky reagent **7** proceeded at a similar rate as the fluorinated analogue, affording the product **8** in 94% de. Product **8** was isolated in 76% yield and its (S_s,3*R*) absolute configuration[26] was determined by comparison

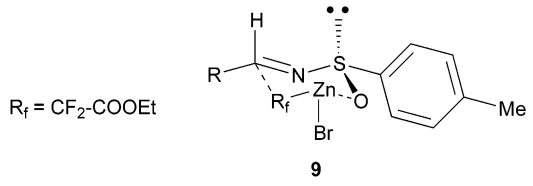

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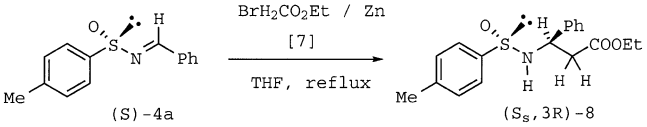
FIGURE 2. Plausible transition state in the Reformatsky reaction.

SCHEME 3



of the optical rotation with the literature data.[14c] These results suggested that the fluorine atoms in reagent **3** have no effect on the stereochemical outcome of the reactions and the operationally convenient conditions used by us might be of general application for preparing aromatic fluorinated as well as nonfluorinated amino acids.

Finally, we studied the application of this method for the synthesis of aliphatic α,α-difluoro-β-amino acids **2** (Scheme 2). To this end we prepared sulfinimines bearing *n*-alkyl **4g**, isopropyl **4h**, and *tert*-butyl **4i** groups. The reactions between aliphatic sulfinimines **4g**−**i** and Reformatsky reagent **3**, conducted under the standard conditions, proceeded with rates similar to those the aromatic series but with lower diastereoselectivity (Table 1, entries 8−10). Thus products **5g** and **5h** were obtained as major products with 72% de (entries 8, 9), while a bit higher, 76% de, selectivity was observed in the synthesis of the *tert*-butyl-containing derivative **5i** (entry 10).

It is interesting to note that in contrast to the aromatic series, the diastereomers **5g**−**i** and **6g**−**i** can be efficiently separated by column chromatography. Thus, purification of the crude reaction mixtures on silica gel afforded diastereomerically pure **5g**−**i** which were hydrolyzed to free amino acids **2g**−**i**, using the standard procedure (Scheme 2).

Taking into account that the stereochemical outcome of the addition reactions under study, regarding the absolute configuration of the newly formed carbon stereogenic center, is similar[26] to the stereochemical preferences generally observed for the nucleophilic additions to sulfinimines of type **4**,[27] we can construct transition state (TS) **9** (Figure 2) to account for the observed diastereoselectivity. In TS **9** the sulfinimine moiety is of the stereochemically favorable *E*-configuration and reagent **3** in the corresponding carbon−metal form.[18] Considering the steric interactions in TS **9** between the substituent R and difluoromethylene group one can explain the differences in the diastereoselectivity ob-

(25) For various effects of fluorine and fluorine-containing substituents on the stereochemical outcome of the asymmetric reactions see ref 4c, as well as the following original papers: (a) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron* **1996**, *52*, 12433−12442. (b) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima N.; Hayashi, T. *J. Org. Chem.* **1997**, *62*, 3470−3479.

(26) The (*S*)-configuration of amino acids **2**, a consequence of the Cahn−Ingold−Prelog priority, is stereochemically equivalent to the (*R*)-configuration in the hydrocarbon series: Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

(27) (a) Hose, D.; Mahon, M.; Molloy, K.; Raynham, T.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 691. (b) Davis, F.; Portonovo, P.; Reddy, R.; Chiu, Y.-H. *J. Org. Chem.* **1996**, *61*, 440. (c) Davis, F.; Fanelli, D. *J. Org. Chem.* **1998**, *63*, 1981. (d) Cogan, D.; Ellman, J. *J. Am. Chem. Soc.* **1999**, *121*, 268.

served in the aromatic and aliphatic series. Thus, when the substituent R is a phenyl group it can minimize the unfavorable steric interactions by virtue of its flat shape. On the other hand, in the case where the R group is a bulky alkyl group it might experience repulsive steric interactions with the difluoromethylene group destabilizing TS **9**.[28]

Conclusion

In summary, we have developed a convenient, synthetically useful procedure for preparing α,α-difluoro-β-amino acids via Reformatsky-type addition reaction between enantiopure *p*-toluenesulfinimines and ethyl bromodifluoroacetate. High chemical and stereochemical yields (drs > 9:1, and as high as 99:1) render this method synthetically superior over previously reported approaches and immediately useful for preparing the target amino acids.

Experimental Section

General. Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. Unless indicated, ^{1}H, ^{19}F, and ^{13}C NMR spectra were taken in $CDCl_3$ solutions at 299.95, 282.24, and 75.42 MHz, respectively, on an instrument in the University of Oklahoma NMR Spectroscopy Laboratory. Chemical shifts refer to TMS and $CFCl_3$ as the internal standards. Optical rotations were recorded on an instrument available at the University of Oklahoma.

Yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H and ^{19}F NMR spectrometry. All new compounds were characterized by ^{1}H, ^{13}C NMR, mass spectrometry (HRMS), and/or elemental analysis.

THF was distilled from sodium/benzophenone immediately before use. Commercial zinc powder was activated by successive washes with 5% hydrochloric acid, water, acetone, and anhydrous ether. Reformatsky reactions were carried out in flame-dried glassware. Column chromatography was carried out with Merck 60 (230−400 mesh) silica gel. Enantiomeric purity of amino acids was determined by ligand-exchange HPLC according to the previously described procedure.[24] Sulfinimines (*S*)-**4a**−**i** were prepared as previously described.[17]

(*S*)-*N*-Benzylidene-*p*-toluenesulfinamide (4a):[17] ^{1}H NMR δ 2.40 (s, 3H), 7.31 (d, J = 8.1 Hz, 2H), 7.45−7.51 (m, 3H), 7.64 (d, J = 8.1 Hz, 2H), 7.83−7.86 (m,2H), 8.75 (s, 1H).

(*S*)-*N*-(*p*-Methoxybenzylidene)-*p*-toluenesulfinamide (4b):[17] ^{1}H NMR δ 2.39 (s, 3H), 3.85 (s, 3H), 6.94 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), 8.68 (s, 1H).

(*S*)-*N*-(*p*-Fluorobenzylidene)-*p*-toluenesulfinamide (4c):[17] ^{1}H NMR δ 2.40 (s, 3H), 7.11−7.16 (m, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.83−7.88 (m, 2H), 8.71 (s, 1H). ^{19}F NMR δ −106.08 (m).

(*S*)-*N*-(*p*-Chlorobenzylidene)-*p*-toluenesulfinamide (4d): eluent = hexanes−ethyl acetate 10:1; yield 78%; mp 118−119 °C; $[\alpha]^{20}_D$ +56.6 (*c* 1.24, CHCl3). ^{1}H NMR δ 2.40 (s, 3H), 7.32 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 8.71 (s, 1H).

(*S*)-*N*-(*p*-Trifluoromethylbenzylidene)-*p*-toluenesulfinamide (4e):[17] ^{1}H NMR δ 2.41 (s, 3H), 7.33 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 8.1 Hz, 2H), 8.79 (s, 1H). ^{19}F NMR δ −63.56 (s).

(*S*)-*N*-(2-Furylmethylidene)-*p*-toluenesulfinamide (4f):[17] ^{1}H NMR δ 2.39 (s, 3H), 5.56 (dd, J = 1.7 and 3.6 Hz, 1H), 7.03 (d, J = 3.6 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.63 (m, 1H), 8.57 (s, 1H).

(*S*)-*N*-(Hexylidene)-*p*-toluenesulfinamide (4g): eluent = hexanes−ethyl acetate 10:1; yield 76%; $[\alpha]^{20}_D$ +322.8 (*c* 1.21, CHCl3). ^{1}H NMR δ 0.87 (t, J = 6.7 Hz, 3H), 1.25−1.34 (m, 4H), 1.56−1.65 (m, 2H), 2.40 (s, 3H), 2.48 (td, J = 7.5 and 5.0 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 8.22 (t, J = 5.0 Hz, 1H).

(*S*)-*N*-(2-Methylpropylidene)-*p*-toluenesulfinamide (4h):[17] ^{1}H NMR δ 1.14 (d, J = 6.9 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 2.40 (s, 3H), 2.60−2.75 (m, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 8.14 (d, J = 4.8 Hz, 1H).

(*S*)-*N*-(2,2-Dimethylpropylidene)-*p*-toluenesulfinamide (4i):[17] ^{1}H NMR δ 1.14 (s, 9H), 2.40 (s, 3H), 7.30 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 8.09 (s, 1H).

Reformatsky Reactions between Sulfinimines (*S*)-4a−i and Ethyl Bromodifluoroacetate. Synthesis of *p*-Toluenesulfinamides 5a−i. (S_s,3*S*)-Ethyl *N*-(*p*-Tolylsulfinyl)-3-amino-2,2-difluoro-3-phenylpropanoate (5a). Typical Procedure. A solution of (*S*)-*N*-benzylidene-*p*-toluenesulfinamide **4a** (243 mg, 1.0 mmol) and ethyl bromodifluoroacetate (0.26 mL, 410 mg, 2.0 mmol) in THF (2 mL) was added dropwise to a refluxing suspension of Zn dust (131 mg, 2.0 mmol) in THF (5 mL). After refluxing for 15 min the reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl, and diluted with ethyl acetate. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography (hexanes−ethyl acetate 3:1) to give 301 mg (yield 82%) of **5a** (as a mixture with **6a** in a ratio of 96:4). Compound **5a** was obtained in a diastereomerically pure form by crystallization of the crude mixture from hexanes−ethyl acetate; 239 mg (65%); mp 119−120° C; $[\alpha]^{20}_D$ +116.2 (*c* 1.04, CHCl3). ^{1}H NMR δ 1.18 (t, J = 7.2 Hz, 3H), 2.43 (s, 3H), 4.09−4.26 (m, 2H), 4.88−5.02 (m, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.38−7.43 (m, 5H), 7.57 (d, J = 8.2 Hz, 2H). ^{13}C NMR δ 162.39 (t, J = 31.1), 141.76, 141.02, 133.21, 129.56, 129.20, 128.72, 128.65, 125.52, 113.78 (t, J = 256), 63.26, 59.69 (t, J = 23.6), 21.48, 13.77. ^{19}F NMR δ −112.58 (dd, J = 256.0 and 11.8 Hz, 1F), −114.74 (dd, J = 256.0 and 12.2 Hz, 1F). Anal. Calcd for $C_{18}H_{19}F_2NO_3S$: C, 58.84; H, 5.21; N, 3.81. Found: C, 58.57; H, 5.49; N, 3.85.

(R_s,3*R*)-Ethyl *N*-(*p*-tolylsulfinyl)-3-amino-2,2-difluoro-3-phenylpropanoate (5a): mp 112−114° C; $[\alpha]^{20}_D$ −111.8 (*c* 1.05, $CHCl_3$). ^{1}H, ^{13}C, ^{19}F NMR spectra are identical with the data reported for (S_s,3*S*)-**5a**.

(S_s,3*S*)-Ethyl *N*-(*p*-tolylsulfinyl)-3-amino-2,2-difluoro-3-(*p*-methoxyphenyl)propanoate (5b): yield 78%; mp 115−116° C; $[\alpha]^{20}_D$ +120.0 (*c* 1.10, $CHCl_3$). ^{1}H NMR δ 1.20 (t, J = 7.2 Hz, 3H), 2.43 (s, 3H), 3.82 (s, 3H), 4.10−4.26 (m, 2H), 4.80 (d, J = 6.7 Hz, 1H), 4.87−4.98 (m, 1H), 6.92 (d, J = 8.2 Hz, 2H), 7.31−7.37 (m, 4H), 7.57 (d, J = 8.2 Hz, 2H). ^{19}F NMR δ −112.10 (dd, J = 255 and 11.9 Hz, 1F), −115.81 (dd, J = 255 and 13.1 Hz, 1F). Anal. Calcd for $C_{19}H_{21}F_2NO_4S$: C, 57.43; H, 5.33; N, 3.53. Found: C, 57.19; H, 5.29; N, 3.27.

(S_s,3*S*)-Ethyl *N*-(*p*-tolylsulfinyl)-3-amino-2,2-difluoro-3-(*p*-fluorophenyl)propanoate (5c): yield 66%; mp 118−120 °C; $[\alpha]^{20}_D$ +98.8 (*c* 0.88, $CHCl_3$). ^{1}H NMR δ 1.20 (t, J = 7.1 Hz, 3H), 2.44 (s, 3H), 4.10−4.27 (m, 2H), 4.87−4.99 (m, 2H), 7.07−7.13 (m, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.39−7.44 (m, 2H), 7.56 (d, J = 8.0 Hz, 2H). ^{13}C NMR δ 162.94 (d, J = 247 Hz), 162.21 (t, J = 30.5 Hz), 141.84, 140.67, 130.67, 130.56, 129.58, 125.48, 115.70 (d, J = 21.4 Hz), 113.60 (t, J = 25.5 Hz), 63.32, 58.75 (t, J = 23.9 Hz), 21.46, 13.78. ^{19}F NMR δ −112.29 (m, 1F), −112.87 (dd, J = 256 and 9.1 Hz, 1F), −114.76 (dd, J = 256 and 12.0 Hz, 1F). Anal. Calcd for $C_{18}H_{18}F_3NO_3S$: C, 56.10; H, 4.71; N, 3.64. Found: C, 56.07; H, 4.69; N, 3.60.

(28) As suggested by the referee, the insignificant differences in the diastereoselectivity observed in the aliphatic series can be accounted for by the high-temperature reaction conditions required for these addition reactions.

(*S*s,3*S*)-Ethyl *N*-(*p*-tolylsulfinyl)-3-amino-2,2-difluoro-3-(*p*-chlorophenyl)propanoate (5d): yield 68%; mp 138−139 °C; $[\alpha]^{20}_D$ +117.8 (*c* 1.46, $CHCl_3$). ^{1}H NMR δ 1.21 (t, J = 7.0 Hz, 3H), 2.43 (s, 3H), 4.10−4.23 (m, 2H), 4.85−4.96 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.37 (s, 4H), 7.55 (d, J = 8.1 Hz, 2H). ^{19}F NMR δ −113.08 (dd, J = 258 and 12.5 Hz, 1F), −114.10 (dd, J = 258 and 10.5 Hz, 1F). Anal. Calcd for $C_{18}H_{18}ClF_2NO_3S$: C, 53.79; H, 4.51; N, 3.49. Found: C, 53.57; H, 4.67; N, 3.40.

(*S*s,3*S*)-Ethyl *N*-(*p*-tolylsulfinyl)-3-amino-2,2-difluoro-3-(*p*-trifluoromethylphenyl)propanoate (5e): yield 57%; mp 150−151 °C; $[\alpha]^{20}_D$ +114.6 (*c* 1.56, $CHCl_3$). ^{1}H NMR δ 1.21 (t, J = 7.1 Hz, 3H), 2.45 (s, 3H), 4.11−4.29 (m, 2H), 4.91−5.03 (m, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.54−7.57 (m, 4H), 7.67 (d, J = 8.2 Hz, 2H). ^{13}C NMR δ 162.14 (t, J = 30.5 Hz), 142.06, 140.33, 137.55, 131.24 (q, J = 3.28 Hz), 129.68, 129.13, 123.70 (q, J = 273 Hz), 113.39 (t, J = 257 Hz), 63.53, 58.86 (t, J = 23.9 Hz), 21.51, 13.77. ^{19}F NMR δ −63.31 (s, 3F), −112.41 (dd, J = 260 and 10.8 Hz, 1F), −114.17 (dd, J = 260 and 13.3 Hz, 1F). Anal. Calcd for $C_{19}H_{18}F_5NO_3S$: C, 52.41; H, 4.17; N, 3.22. Found: C, 52.26; H, 4.12; N, 3.08.

(*S*s,3*S*)-Ethyl *N*-(*p*-tolylsulfinyl)-3-amino-2,2-difluoro-3-(2-furyl)propanoate (5f): yield 49%; mp 98−99 °C; $[\alpha]^{20}_D$ +101.1 (*c* 0.79, $CHCl_3$). ^{1}H NMR δ 1.24 (t, J = 7.1 Hz, 3H), 2.43 (s, 3H), 4.11−4.31 (m, 2H), 4.91−5.04 (m, 2H), 6.39 (dd, J = 3.1 and 1.8 Hz, 1H), 6.43 (d, J = 3.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.45 (m, 1H), 7.58 (d, 8.2 Hz, 2H). ^{19}F NMR δ −113.14 (m). Anal. Calcd for $C_{16}H_{17}F_2NO_4S$: C, 53.78; H, 4.79; N, 3.92. Found: C, 53.47; H, 4.90; N, 3.58.

(*S*s,3*S*)-Ethyl *N*-(*p*-tolylsulfinyl)-3-amino-2,2-difluorooctanoate (5g): eluent = methylene chloride−acetone 10:0.1; yield 59% (semisolid); $[\alpha]^{20}_D$ +40.8 (*c* 1.03, $CHCl_3$). ^{1}H NMR δ 0.92 (t, J = 7.1 Hz, 3H), 1.26−1.81 (m, 8H), 1.35 (t, J = 7.2 Hz, 3H), 2.42 (s, 3H), 3.78−3.93 (m, 1H), 4.24−4.41 (m, 3H), 7.31 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H). ^{19}F NMR δ −111.21 (dd, J = 262 and 8.2 Hz, 1F), −117.15 (dd, J = 262 and 15.5 Hz, 1F). Anal. Calcd for $C_{17}H_{25}F_2NO_3S$: C, 56.49; H, 6.97; N, 3.88. Found: C, 56.43; H, 6.81; N, 3.85.

Minor diastereomer (*S*s,3*R*)-**6g**: yield 8%; mp 55−57 °C; $[\alpha]^{20}_D$ +97.7 (*c* 0.84, CHCl3). ^{1}H NMR δ 0.89 (t, J = 6.8 Hz, 3H), 1.26−1.85 (m, 8H), 1.38 (t, J = 7.2 Hz, 3H), 2.41 (s, 3H), 3.90−4.01 (m, 1H), 4.38 (q, J = 7.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H).^{19}F NMR δ −111.52 (dd, J = 259 and 7.0 Hz, 1F), −119.79 (dd, J = 259 and 16.2 Hz, 1F). Anal. Calcd for $C_{17}H_{25}F_2NO_3S$: C, 56.49; H, 6.97; N, 3.88. Found: C, 56.02; H, 7.10; N, 3.53.

(*S*s,3*S*)-Ethyl *N*-(*p*-tolylsulfinyl)-3-amino-2,2-difluoro-4-methylpentanoate (5h): eluent = hexanes−ethyl acetate 4:1; yield 65%; $[\alpha]^{20}_D$ +72.7 (*c* 0.99, $CHCl_3$). ^{1}H NMR δ 0.94 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H), 2.14−2.25 (m, 1H), 2.42 (s, 3H), 3.78−3.92 (m, 1H), 4.09−4.23 (9m, 2H), 4.30 (d, J = 10.5 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.1 Hz, 2H). ^{19}F NMR δ −110.04 (dd, J = 262 and 7.8 Hz, 1F), −114.87 (dd, J = 262 and 17.8 Hz, 1F). Anal. Calcd for $C_{15}H_{21}F_2NO_3S$: C, 54.04; H, 6.35; N, 4.20. Found: C, 53.73; H, 6.46; N, 3.86.

Minor diastereomer (*S*s,3*R*)-**5h**: yield 11% (clear oil); $[\alpha]^{20}_D$ +39.0 (*c* 0.41, $CHCl_3$). ^{1}H NMR δ 0.97 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.7 Hz, 3H), 1.38 (t, J = 7.2 Hz, 3H), 2.10−2.21 (m, 1H), 2.41 (s, 3H), 3.81−3.95 (m, 1H), 4.18 (d, J = 10.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H). ^{19}F NMR δ −110.10 (dd, J = 260 and 11.0 Hz, 1F), −116.83 (dd, J = 260 and 21.8 Hz, 1F). Anal. Calcd for $C_{15}H_{21}F_2NO_3S$: C, 54.04; H, 6.35; N, 4.20. Found: C, 54.02; H, 6.28; N, 4.12.

(*S*s,3*S*)-Ethyl *N*-(*p*-tolylsulfinyl)-3-amino-2,2-difluoro-4,4-dimethylpentanoate (5i): eluent = hexanes−ethyl acetate 3:1; yield 60%; $[\alpha]^{20}_D$ +74.4 (*c* 0.90, $CHCl_3$). ^{1}H NMR δ 1.10 (s, 9H), 1.40 (t, J = 7.1 Hz, 3H), 2.42 (s, 3H), 3.79 (ddd, J = 7.5, 10.1 and 19.8 Hz, 1H), 4.29 (d, J = 10.1 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H). ^{19}F NMR δ −104.90 (dd, J = 260 and 7.5 Hz, 1F), −113.49 (dd, J = 260 and 19.8 Hz, 1F). Anal. Calcd for $C_{16}H_{23}F_2NO_3S$: C, 55.31; H, 6.67; N, 4.03. Found: C, 55.25; H, 6.75; N, 3.98.

(*S*s,3*R*)-Ethyl *N*-(*p*-Tolylsulfinyl)-3-amino-3-phenylpropanoate (8).[14] Sulfinamide **8** was prepared from (*S*)-**4a** (243 mg, 1.0 mmol), ethyl bromoacetate (0.222 mL, 334 mg, 2.0 mmol), and Zn (131 mg, 2.0 mmol) in THF (8 mL) according to the procedure described for (*S*s,3*S*)-**2a**. Purification of crude product by flash chromatography (hexanes−ethyl acetate 3:1) afforded 252 mg (yield 76%) of (*S*s,3*R*)-**8** (94% de); mp 58−59 °C; $[\alpha]^{20}_D$ +77.0 (*c* 2.52, $CHCl_3$). ^{1}H NMR δ 1.15 (t, J = 7.1 Hz, 3H), 2.41 (s, 3H), 2.83 (d, J = 6.3 Hz, 2H), 4.05 (q, J = 7.1 Hz, 2H), 4.90 (td, J = 6.3 and 5.2 Hz, 1H), 5.04 (d, J = 5.2 Hz, 1H), 7.29−7.44 (m, 7H), 7.60 (d, J = 8.3 Hz, 2H).

Hydrolysis of Amides 5a−e,g−i to Free Amino Acids 2a−e,g−i. (*S*)-3-Amino-2,2-difluoro-3-phenylpropanoic Acid (2a). Typical Procedure. A solution of diastereomerically pure (*S*s,3*S*)-**5a** (197 mg, 0.54 mmol) in 6 N HCl (11 mL) was refluxed for 4 h. The aqueous phase was washed with ether (2 × 5 mL) and the aqueous solution was concentrated under reduce pressure to dryness. The resulting solid was treated with *i*-PrOH (3 mL) and propylene oxide (0.151 mL, 125 mg, 2.16 mmol) and the reaction mixture was stirred for 5 h. Precipitate was filtered off and washed with ether to provide 95 mg (88%) of amino acid (*S*)-**2a** as a white solid; mp 242−244° C, $[\alpha]^{19}_D$ +7.71 (*c* 0.99, CH_3OH) [lit.[9b] $[\alpha]_D^{25}$ +7.1 (*c* 1.0, MeOH)]. ^{1}H NMR (DMSO-d_6) δ 4.81 (dd, J = 15.0 and 8.4 Hz, 1H), 7.39−7.52 (m, 5H), 9.09 (br s, 3H). ^{13}C NMR (MeOH-d_4) δ 166.67 (t, J = 25.4 Hz), 131.37, 130.91, 129.92, 129.78, 114.99 (t, J = 258 Hz), 58.55 (t, J = 26.0 Hz). ^{19}F NMR (DMSO-d_6) δ −106.00 (dd, J = 260. and 8.4 Hz, 1F), −110.85 (dd, J = 260 and 15.0 Hz, 1F). Anal. Calcd for $C_9H_9F_2NO_2$: C, 53.73; H, 4.51; N, 6.96. Found: C, 53.35; H, 4.21; N, 6.70.

(*S*)-3-Amino-2,2-difluoro-3-(*p*-methoxyphenyl)propanoic acid (2b): yield 96%; mp 261−263 °C. ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3H), 4.74 (dd, J = 14.6 and 8.4 Hz, 1H), 6.97 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 9.05 (br s, 3H). ^{19}F NMR (DMSO-d_6) δ −106.05 (dd, J = 260 and 8.4 Hz, 1F), −110.75 (dd, J = 260 and 14.6 Hz, 1F). Anal. Calcd for $C_{10}H_{11}F_2NO_3$: C, 51.95; H, 4.80; N, 6.06. Found: C, 51.91; H, 5.02; N, 5.86.

(*S*)-3-Amino-2,2-difluoro-3-(*p*-fluorophenyl)propanoic acid (2c): yield 82%; mp 248−250 °C. ^{1}H NMR (DMSO-d_6) δ 4.87 (dd, J = 15.2 and 8.2 Hz, 1H), 7.25−7.31 (m, 2H), 7.54−7.58 (m, 2H), 9.09 (br s, 3H). ^{13}C NMR (MeOH-d_4) δ 166.61 (t, J = 26.2 Hz), 164.75 (d, J = 246 Hz), 132.16 (d, J = 8.48 Hz), 127.50, 116.77 (d, J = 21.9 Hz), 114.94 (t, J = 257 Hz), 57.74 (t, J = 26.8 Hz). ^{19}F NMR (DMSO-d_6) δ −106.09 (dd, J = 262 and 8.2 Hz, 1F), −110.83 (dd, J = 262 and 15.2 Hz, 1F), −112.14 (s, 1F). Anal. Calcd for $C_9H_8F_3NO_2$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.44; H, 3.31; N, 6.09.

(*S*)-3-Amino-2,2-difluoro-3-(*p*-chlorophenyl)propanoic acid (2d):yield 78%; mp >350 °C; $[\alpha]^{20}_D$ +14.5 (*c* 0.81, CH_3OH). ^{1}H NMR (DMSO-d_6) δ 4.86−4.94 (m, 1H), 7.51 (s, 4H), 9.15 (br s, 3H). ^{19}F NMR (DMSO-d_6) δ −106.64 (d, J = 260 Hz, 1F), −110.49 (dd, J = 260 and 9.1 Hz). Anal. Calcd for $C_9H_8ClF_2NO_2$: C, 45.88; H, 3.42; N, 5.94. Found: C, 46.20; H, 3.63; N, 6.04.

(*S*)-3-Amino-2,2-difluoro-3-(*p*-trifluoromethylphenyl)-propanoic acid (2e): yield 94%; mp 252−254 °C. ^{1}H NMR (DMSO-d_6) δ 5.01 (dd, J = 14.6 and 8.8 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.82 (d, J 8.4 Hz, 2H), 9.07 (br s, 3H). ^{13}C NMR (MeOH-d_4) δ 166.36 (t, J = 25.9 Hz), 135.74, 132.81 (q, J = 32.2 Hz), 130.72, 126.77 (q, J = 3.68 Hz), 125.12 (q, J = 269 Hz), 114.82 (t, J = 258 Hz), 57.95 (t, J = 27.0 Hz). ^{19}F NMR (DMSO-d_6) δ −60.74 (s, 3F), −106.22 (dd, J = 260 and 8.8 Hz, 1F), −110.33 (dd, J = 260 and 14.6 Hz, 1F). Anal. Calcd for $C_{10}H_8F_5NO_2$: C, 44.62; H, 2.99; N, 5.20. Found: 44.87; H, 3.18; N, 4.98.

(*S*)-3-Amino-2,2-difluorooctanoic acid (2g): yield 56%; mp 223−225 °C; $[\alpha]^{20}_D$ −9.3 (*c* 0.86, CH3OH). ^{1}H NMR (DMSO-d_6) δ 1.10 (t, J = 6.6 Hz, 3H), 1.42−1.87 (m, 8H), 3.70 (m, 1H), 8.87 (br s, 3H). ^{13}C NMR (DMSO-d_6) 13.82, 21.80, 24.34, 26.81, 30.97, 52.94 (t, J = 27.6 Hz), 114.08 (t, J = 257.8 Hz), 163.70

(t, J = 25.1 Hz). ^{19}F NMR (DMSO-d_6) δ −109.51 (d, J = 262 Hz, 1F), −111.21 (d, J = 262 Hz, 1F). Anal. Calcd for $C_8H_{15}F_2NO_2$: C, 49.22; H, 7.75; N, 7.18. Found: C, 49.30; H, 8.11; N, 6.85.

(*S*)-3-Amino-2,2-difluoro-4-methylpentanoic acid (2h): yield 63%; mp 208−210 °C; $[\alpha]^{20}_D$ +16.0 (*c* 0.50, CH_3OH). ^{1}H NMR (DMSO-d_6) δ 0.96 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 2.02−2.13 (m, 1H), 3.41 (m, 1H), 8.56 (br s, 3H). ^{13}C NMR (DMSO-d_6) δ 17.48, 19.67, 26.50, 57.52 (t, J = 26.1 Hz), 114.40 (t, J = 258.4 Hz), 163.97 (t, J = 25.2 Hz). ^{19}F NMR (DMSO-d_6) δ −106.56 (dd, J = 260 and 12.8 Hz, 1F), −108.02 (dd, J = 260 and 11.2 Hz, 1F). Anal. Calcd for $C_6H_{11}F_2NO_2$: C, 43.12; H, 6.63; N, 8.38. Found: C, 43.34; H, 6.87; N, 8.12.

(*S*)-3-Amino-2,2-difluoro-4,4-dimethylpentanoic acid (2i): yield 70%; mp 225−227 °C; $[\alpha]^{20}_D$ +12.2 (*c* 1.31, CH_3OH). ^{1}H NMR (DMSO-d_6) δ 1.03 (s, 9H), 3.42 (m, 1H), 8.58 (br s, 3H). ^{13}C NMR (DMSO-d_6) δ 26.95, 32.63, 60.08 (t, J = 25.4 Hz), 114.68 (t, J = 260.5 Hz), 164.43 (t, J = 25.2 Hz). ^{19}F NMR (DMSO-d_6) δ −104.22 (dd, J = 260 and 8.0 Hz, 1F), −106.40 (dd, J = 260 and 16.7 Hz, 1F). Anal. Calcd for $C_7H_{13}F_2NO_2$: C, 46.41; H, 7.23; N, 7.73. Found: C, 46.59; H, 7.05; N, 7.82.

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Supporting Information Available: X-ray data for compound **5e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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