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Umpolung Reactivity of Difluoroenol Silyl Ethers with Amines and Amino Alcohols. Application to the Synthesis of Enantiopure α-Difluoromethyl Amines and Amino Acids

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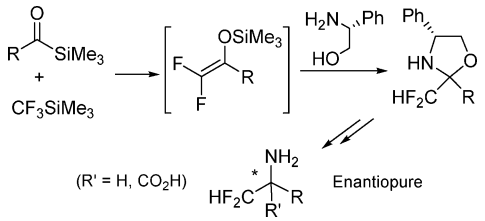

Difluoroenol silyl ethers, produced in situ from acylsilanes and CF_3TMS, react as electrophiles with amines to give difluoroimines, via the corresponding hemiaminal adduct, as evidenced by ^{19}F NMR spectroscopy. Reaction with (*R*)-phenylglycinol led to 2-difluoromethyloxazolidines. After separation of the diastereomers, reduction with LAH and Strecker-type synthesis gave enantiopure α-difluoromethylamines and α-difluoromethyl-α-amino acids, respectively.

Introduction

Enol silyl ethers are important intermediates in organic synthesis. They are used as enolate equivalents, in reactions involving either a nucleophilic activation or the electrophilic activation of the counter reactant (Mukayiama type reactions).[1] Thus, except for particular situations such as single electron oxidation giving the corresponding radical cation,[2] enol silyl ethers are essentially nucleophilic intermediates.

Difluoroenol silyl ethers (DFSE) are also building blocks of great interest for the synthesis of a variety of functionalized difluoromethylene compounds. Owing to its small size and its high electronegativity, the presence of fluorine atoms in organic molecules induces strong modifications of their properties.[3] This effect operates both in the preparation methodologies and in the properties of the final product. Polyfluorinated enol silyl ethers offer a good illustration. The usual methods are not applicable to the preparation of DFSE and higher perfluoroenoxy silane analogues. Most of the methods proposed for the preparation of DFSE start from fluorinated substrates.[4] We have proposed another approach with final introduction of fluorine via reaction of fluoroorganometallic reagents on acylsilanes, using either trifluoromethyl(trimethyl)silane or perfluoroorganolithium for the preparation of DFSE[5] or higher homologues,[6]

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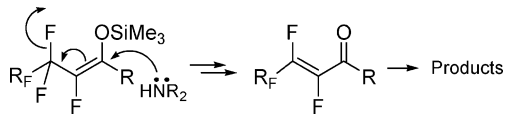
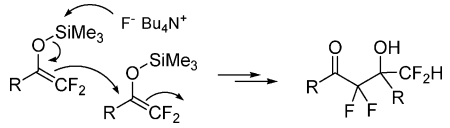
SCHEME 1. S_N'-Type Reaction of Perfluoroenoxysilanes



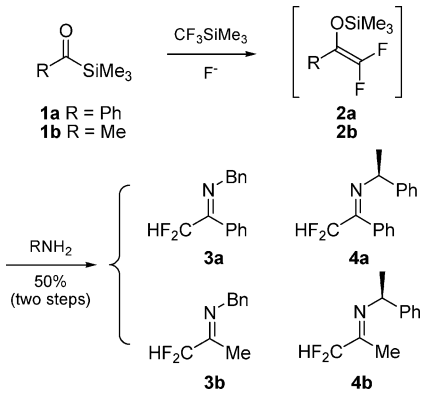
SCHEME 2. Self-Condensation Reaction of Difluoroenol Silyl Ethers



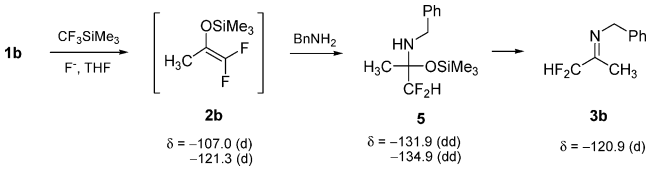
respectively. DFSE exhibit the classical nucleophilic reactivity of non-fluorinated analogues. Acid hydrolysis,[5] halogenation,[7] and Lewis acid-promoted reactions with various electrophiles[8] afforded a wide variety of applications in the synthesis of *gem*-difluoromethylene compounds. We had mentionned the Mukayiama-type aldol reaction of higher homologues,[6] but these enol silyl ethers were essentially used as key intermediates in the synthesis of polyfluorinated β-enaminoketones and heterocycles,[9] via an hemifluorinated enone.[10] In these transformations, perfluoroenol silyl ethers behave as powerful electrophilic substrates, in an S_N'-type displacement of the β-fluorine induced by the attack of the silyloxy substituted carbon by the amine (Scheme 1).

We reported in our initial paper the formation of a self-condensation product of DFSE (Scheme 2).[5] According to our preparation methodology, DFSE is the result of a chain reaction involving the domino sequence: nucleophilic trifluoromethylation of an acylsilane−Brook rearrangement−fluoride elimination. Depending on the nucleophilicity of the fluoride initiator, the DFSE is the final product of this chain process or its fluoride activation leads to a difluoroenolate which adds to another molecule of DFSE (Scheme 2). That was the very first observation of the electrophilic behavior of nonoxidized DFSE. Very recently, it was shown that, under single electron oxidative conditions, the polarity of DFSE can also be reversed.[11] We report in this paper on our investigation on the umpolung reactivity of unmodified DFSE with amines and amino alcohols and its application to the synthesis of α-difluoromethyl amino derivatives.

SCHEME 3. Reaction of DFSE 2a and 2b with Primary Amines



SCHEME 4. ^{19}F NMR Monitoring of Addition of Benzylamine on 2b



Results and Discussion

The reaction of DFSE **2a** (generated in situ from acylsilane **1a** (Scheme 3)) with amines depends on the nature of the amine. Triethylamine led to the self-condensation product and thus acts similarly to TBAF as a nucleophilic activator. The sole product observed with secondary amines was the difluoromethylketone, the formal result of the hydrolysis of **2a**, even if a direct decomposition of an intermediate aminal (vide infra) cannot be excluded. Much more interestingly, primary amines react slowly with **2a** in a formal addition−elimination process to give the corresponding difluoromethyl imines. Similar results were observed from **2b** and/or with other amines, giving the imines **3** and **4** (Scheme 3). These imines are of limited stability and were difficult to isolate and characterize. Authentic samples were prepared conventionally, in high yield, from the difluoromethyl ketone obtained by direct hydrolysis of the intermediate DFSE. To discriminate between an actual addition−elimination sequence and a possible in situ hydrolysis of the DFSE followed by a classical amination of the resulting difluoromethyl ketone, we have carefully monitored the reaction by ^{19}F NMR spectrometry. When **2b**, generated in situ from acetyl(trimethyl)-silane **1b**, is treated with benzylamine, we were unable to detect any trace of difluoromethylketone, but the NMR monitoring clearly shows the intermediate formation of the hemiaminal adduct **5**, and its slow conversion into the ketimine **3b** (Scheme 4). Thus, DFSE acts definitely as an electrophilic species.

To diversify the difluoromethyl intermediates, especially toward applications in asymmetric synthesis, we have extended the reaction to chiral amino alcohols, in order to have access to chiral difluoromethyl oxazolidines. Oxazolidines proved indeed to be interesting building blocks in the trifluoromethyl series (vide infra). The reaction of **2a** with (*R*)-phenylglycinol gave oxazolidine **6a** with a high yield and a poor diastereoselectivity (Scheme 5).

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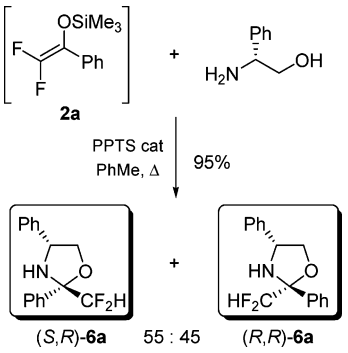
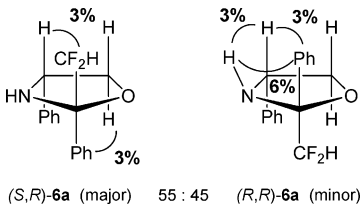
(11) Uneyama, K.; Tanaka, H.; Kobayashi, S.; Shioyama, M.; Amii, H. *Org. Lett.* **2004**, *6*, 2733−2736.

SCHEME 5. Synthesis of 2-Difluoromethyl Oxazolidines from 2a



SCHEME 6. NOE Data for Oxazolidine 6a



This transformation requires heating in toluene, a solvent not adapted to the previous step. Thus, the DFSE **2a** was prepared in ether, which was removed under vacuum and replaced by toluene. Addition of phenylglycinol and a catalytic amount of pyridinium *p*-toluenesulfonate, and heating to reflux afforded the product in high yield. The two diastereomers were easily separated over silica gel, giving two diastereopure intermediates (*S*,*R*)-**6a** and (*R*,*R*)-**6a** of high potential for further transformations (see below). The configuration of the diastereomers were determined by NOE experiments (Scheme 6).

The similar treatment of **2b**, prepared in situ from **1b**, afforded quantitatively the corresponding imine **7** as its *O*-silyl ether (Scheme 7). It is worth noting that this imine formation is more effective and faster than with simple amines. The fast shift of the equilibrium toward the product is probably due to an irreversible silylation of the hydroxyl group by competitive trapping of TMSOH or intramolecular TMS transfer. This process constitutes an effective one-pot preparation of the imine **7** from three commercially available starting compounds: acetyltrimethylsilane, trifluoromethyltrimethylsilane, and phenylglycinol. The silylated iminoether **7** was easily converted to the corresponding oxazolidine **6b** by desilylation−cyclization (Scheme 7). The oxazolidine **6b** was obtained with a remarkable overal yield of 92% from acetyltrimethylsilane, as an 85/15 mixture of nonseparable diasteromers (*S*,*R*)-**6b** and (*R*,*R*)-**6b**, the configuration of which has been determined by NOE experiments. Benzoylation of **6b** afforded the easily separated *N*-benzoyl derivatives (*S*,*R*)-**9b** and (*R*,*R*)-**9b**.

The interest of imine and oxazolidine as intermediates in asymmetric organofluorine synthesis has been disclosed by several reports. A chirality transfer via a base-induced 1,3-proton shift on chiral imine was achieved by Soloshonok.[12] Asymmetric preparation of α-perfluoroalkylamines was first achieved by Pirkle by reduction of the corresponding imines derived from (*S*)-α-methylbenzylamine.[13] Mikami reported the highly stereoselective organometallics addition and reduction of trifluoromethyl imines and 2-trifluoromethyl oxazolidines derived from (*R*)-phenylglycinol.[14] The iminum-type reactivity of the (*R*)-phenylglycinol based oxazolidines and its application to the synthesis of enantiopure trifluoromethylated amines, α- and *β*-amino acids, *β*-amino ketones, and *β*- and *γ*-amino alcohols was more recently reported.[15] The difluoromethyl series was approached recently, via organometallic arylation of oxazolidine-derived chiral imines,[16] or via diastereoselective reduction of α-difluoromethylimine derived from (*S*)-α-phenylethylamine followed by a regioselective hydrogenolysis.[17]

Our attempts to prepare optically active α-difluoroamines via a base induced proton shift from the imine **4a** failed. The strong base (DBU) required for this reaction induced a fluoride elimination.

To assess the usefulness of this DFES methodology for the synthesis of enantiopure α-difluoromethylamines, the difluoromethyl imino and oxazolidino intermediates described above were submitted to $LiAlH_4$ reduction. Poor to fair yields and/or diastereoselectivity were observed from the difluoroimines **4**. In contrast, reduction of diastereomerically pure oxazolidines (*S*,*R*)-**6a** and (*R*,*R*)-**6a** afforded the corresponding amino alcohols (*R*,*R*)-**10a** and (*S*,*R*)-**10a** with a total stereoselectivity (Scheme 8). According to the previous observations of Mikami in the trifluoromethyl series,[14] we reasonably consider here too a retention of the configuration of the functional carbon due to the coordination of oxygen to the metal.

Oxidative cleavage of the intermediate amino alcohols (*R*,*R*)-**10a** and (*S*,*R*)-**10a** led to the corresponding imines **11a**, the acid hydrolysis of which afforded the two enantiomers of 2,2-difluoro-1-phenylethylamine (*R*)-**12a** and (*S*)-**12a**. The enantiomeric relationship is confirmed by their opposite optical rotation. The stereoselectivity of the reduction and the resulting configuration of the final amine is corroborated by a recent report on the synthesis of similar amines by a different methodology.[18]

Racemic difluoroisopropylamine has been known for a long time.[19] The synthesis of its enantiopure hydrochloride (*R*)-**12b** was achieved by palladium catalyzed hydrogenolysis of the bis-(benzylic) intermediates (*R*,*R*)-**13b** derived from the LAH reduction of (*S*,*R*)-**9b** (Scheme 9). This LAH reduction proceeded in two steps with a faster reduction of the benzoyl moiety. The intermediate *N*-benzyloxazolidine **14** has been isolated during the partial reduction of (*R*,*R*)-**9b** with shorter reaction time. The enantiomer (*S*)-**12b**could of course be prepared similarly from the parent diastereomer (*S*,*R*)-**13b** obtained in 72% yield from (*R*,*R*)-**9b.**

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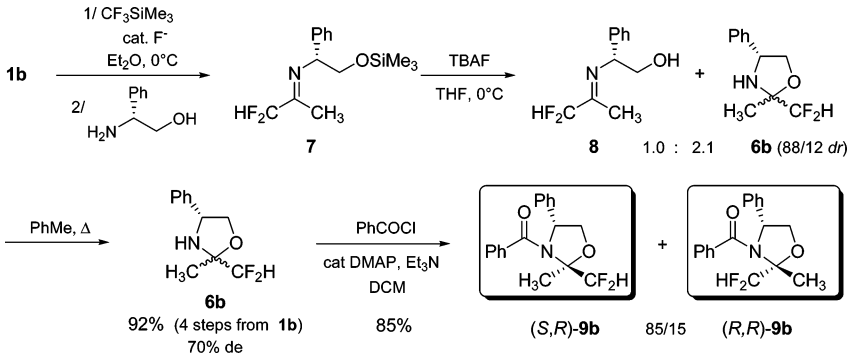
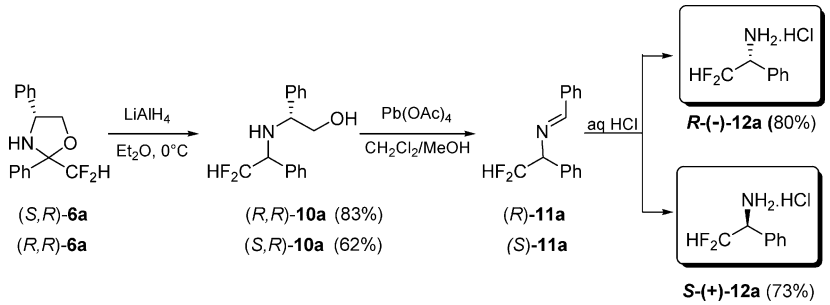
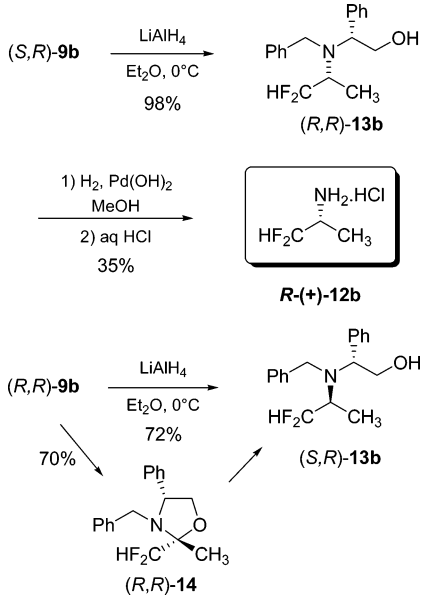
SCHEME 7. Synthesis of 2-Difluoromethyloxazolidines from 1b



SCHEME 8. Synthesis of Enantiopure 2-Difluoromethyl(ethyl)amine

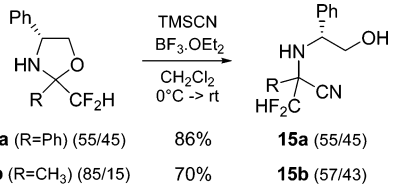


SCHEME 9. Synthesis of Enantiopure 2-Difluoromethyl(ethyl)amine 12b



The Strecker reaction (hydrocyanation of imines)[20] and its asymmetric variant[21] is a well-known process for the conversion of aldehydes and ketones into α-amino acids. Hydro- or silylcyanation of chiral amino alcohol derived imines/oxazolidines was already described.[22] The asymmetric synthesis of

SCHEME 10. Synthesis of Difluoro Amino Nitriles 15a,b



trifluoroalanine and trifluoromethylalanine from the 2-trifluromethyl oxazolidines derived from phenylglycinol and fluoral and trifluoroacetone was reported recently.[15a,c] Thus, we have investigated a second important application of the electrophilic behavior of DFSE: the synthesis of enantiopure α-difluoromethyl-α-amino acids, via a Strecker-type reaction using the difluoromethyl imines and/or oxazolidines. The cyanosilylation of the imines was successful, but suffers from the difficulty to separate the aminonitriles diastereomers. Here again, the starting material of choice proved to be the difluoromethyl oxazolidines. Under Lewis acid activation (BF_3·OEt_2), cyanosilylation of compounds **6a**,**b** proceeded with good yield and poor diastereoselectivity, yielding the cyano amino alcohols **15a**,**b**, respectively (Scheme 10). In particular, the different diastereomeric ratio for compounds **6b** and **15b** is in accordance with the addition of the cyanide on an intermediate iminium salt. The diastereomers were easily separated by chromatography, opening a way for the preparation of both enantiomers of the corresponding amino acid from a unique amino alcohol auxiliary.

The conversion of the aromatic derivative **15a** into the corresponding amino acid failed. Its acid hydrolysis led to the difluoromethyl ketone via a sequence dehydrocyanation-hydrolysis. In contrast, the two diastereomers (*R*,*R*)-**15b** and (*S*,*R*)-**15b** derived from acetyltrimethylsilane were converted, via the hydrochlorides **17**, into the two enantiomers of 2-difluoromethyl alanine (*R*)-**18** and (*S*)-**18** (Scheme 11). The configuration of each enantiomer was easily ascribed according to the reported enantiomer (*R*)-**18**,[23] allowing the determination of the config-

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(21) (a) Williams, R. M. *Synthesis of Optically active α-Amino Acids*; Pergamon Press: Oxford, 1989; Chapter 5, p 208. (b) Duthaler, O. R. *Tetrahedron* **1994**, *50*, 1539−1650. (c) Grôger, H. *Chem. Rev.* **2003**, *103*, 2795−2828. (d) Connon, S. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1176−1178.
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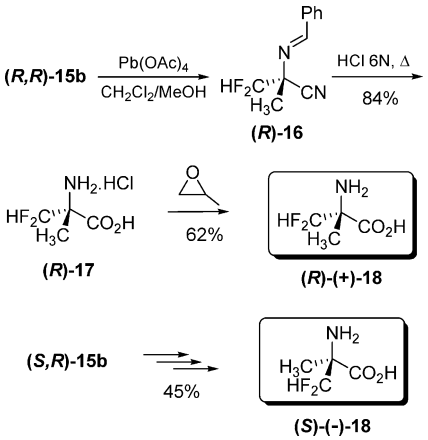
SCHEME 11. Synthesis of Enantiopure 2-Difluoromethylalanine 18



uration of the diastereomeric precursors (*R*,*R*)-**15b** and (*S*,*R*)-**15b**. This correlation indicates that the course of the cyanosilylation is similar to the one described by Chakraborty et al. in the nonfluorinated series.[22a]

Conclusion

In summary, difluoroenol silyl ethers can behave as electrophilic reactant with amines and amino alcohols, giving rise to difluoromethyl imines and oxazolidines, respectively. The use of (*R*)-phenylglycinol allowed to prepare diastereomerically pure 2-difluoromethyl oxazolidines which proved to be good precursors toward enantiopure α-difluoromethyl amines (by LAH reduction), or α-difluoromethyl alanine (via a Strecker reaction). The key 2-difluoromethyl oxazolidine intermediates are prepared in high yield from acylsilanes, successively treated with trifluoromethyltrimethylsilane and the amino alcohol reagent. This methodology is of great interest, in particular in the aliphatic series, where the preparation of DFSE by Mg reduction/silylation of trifluoromethyl ketones[4c] is much less effective than in aromatic series.

After their numerous applications as enolate equivalents, the possibility of DFSE to react with nucleophilic amines considerably extends their potential as *gem*-difluoro building blocks.

Experimental Section

Synthesis of 2-Difluoromethyloxazolidine 6a. To a stirred solution of benzoyl(trimethyl)silane **1a** (1.07 g, 6.0 mmol, 1.0 equiv) in diethyl ether (15 mL) at 0 °C were added CF_3SiMe_3 (1.4 mL, 7.4 mmol, 1.23 equiv) and $nBu_4N^+Ph_3SnF_2^-$ (34 mg, 0.23 mmol, 0.01 equiv). After complete conversion (GC), the resulting mixture was filtered and concentrated to afford difluoroenol silyl ether **2a** (1.37 g), which was dissolved in toluene (40 mL). (*R*)-Phenylglycinol (6.0 mmol, 0.90 g, 1.0 equiv) and pyridinium p-toluenesulfonate (0.60 mmol, 0.91 g, 0.1 equiv) were added, and the mixture was heated to reflux with a Dean−Stark apparatus for 24 h under argon and then cooled to 0 °C with an ice bath. The resulting mixture was filtered on Celite, and toluene was evaporated. Separation by flash chromatography (19:1 petroleum ether/ethyl acetate) afforded (*S*,*R*)-**6a** (0.87 g, 50%) and (*R*,*R*)-**6a** (0.70 g, 45%) as yellow oils.

(2*S*,4*R*)-2-Difluoromethyl-2,4-diphenyl-1,3-oxazolidine (*S*,*R*)-6a: $[\alpha]^{20}_D$ +14.7 (*c* 0.74, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.63 (d, 1H, $^3J_{HH}$ = 8.0), 3.78 (dd, 1H, $^3J_{HH}$ = 8.7, $^2J_{HH}$ = 7.9), 4.56 (dd, 1H, $^2J_{HH}$ = 8.7, $^3J_{HH}$ = 6.7), 4.71 (ddd, 1H, $^3J_{HH}$ = 8.0, 7.9, 6.7), 5.87 (t, 1H, $^2J_{HF}$ = 55.6), 7.2−7.5 (m, 8H), 7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 62.4, 72.9, 96.5 (t, $^2J_{CF}$ = 22.5), 115.1 (t, J_{CF} = 250.9), 125.9, 126.7, 128.0, 128.4, 128.7, 128.9, 137.9, 138.0; ^{19}F NMR ($CDCl_3$) δ −128.6 (dd,1F, $^2J_{FF}$ = 275.5, $^2J_{HF}$ = 55.6), −130.9 (dd, 1F, $^2J_{FF}$ = 275.5, $^2J_{HF}$ = 55.6).

(2*R*,4*R*)-2-Difluoromehyl-2,4-diphenyl-1,3-oxazolidine (*R*,*R*)-6a: $[\alpha]^{20}_D$ −86.8 (*c* 0.84, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.94 (br, 1H), 3.94 (m, 1H), 4.5 (m, 2H), 5.85 (t, 1H, $^2J_{HF}$ = 55.6), 7.2−7.5 (m, 8H), 7.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 60.7, 72.9, 96.0 (t, $^2J_{CF}$ = 22.5), 114.6 (t, J_{CF} = 250.5), 126.6, 126.7, 127.8, 128.2, 128.6, 128.7, 137.9, 138.8; ^{19}F NMR ($CDCl_3$) δ −129.0 (dd, 1F, $^2J_{FF}$ = 277.4, $^2J_{HF}$ = 55.6), −131.5 (dd, 1F, $^2J_{FF}$ = 277.4, $^2J_{HF}$ = 55.6); IR (neat) ν 3354, 3061, 2972, 1450, 1435, 1074; MS (EI 70 eV) *m*/*z* 276 (M + 1), 245, 224 (100), 193, 165, 104. Anal. Calcd for $C_{16}H_{15}F_2NO$: C, 69.81; H, 5.49; N, 5.09. Found: C, 69.46; H, 5.61; N, 4.80.

Synthesis of 2-Difluoromethyloxazolidine 6b and Their *N*-Benzoyl Derivatives 9b. Difluoroenol silyl ether **2b** was prepared similarly from acetyl(trimethyl)silane **1b** and treated in situ at 0 °C with (*R*)-phenylglycinol to give quantitatively, in 3h, (*E*)-2,2-difluoro-1-methylethylidene((1*R*)-2-trimethylsilyloxy-1-phenylethyl)amine **7** as a yellowish oil. To a stirred solution of ketimine **7** (2.85 g, 10.0 mmol, 1.0 equiv) in 10 mL of THF under argon at 0 °C was added TBAF (3.2 g, 10.0 mmol, 1.0 equiv). After consumption of starting material, the mixture was poured into a saturated $NaHCO_3$ solution. After extraction with Et_2O (4 × 20 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a mixture of the desilylated ketimine **8** and oxazolidine **6b (**7.3:1 mixture of diastereomers).

A stirred solution of the mixture **8** + **6b** in 60 mL of toluene was heated to reflux overnight. After the solution was cooled to 0 °C with an ice bath, the resulting mixture was concentrated under reduced pressure. Purification by flash chromatography (9:1 petroleum ether /ethyl acetate) gave 1.96 g (92% from **2b**) of a 5.7:1 mixture of diasteromers **6b** as a yellow oil. To a stirred solution of **6b** (0.64 g, 3.0 mmol, 1.0 equiv) in dichloromethane (10 mL) cooled to 0 °C were added triethylamine (0.63 mL 4.5 mmol, 1.5 equiv), DMAP (0.55 g, 4.5 mmol, 1.5 equiv), and benzoyl chloride (0.53 mL, 4.5 mmol, 1.5 equiv). After complete consumption of starting material, the mixture was filtered on Celite and washed with Et_2O. The organic layer was extracted once with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Separation by flash chromatography (9:1 petroleum ether /ethyl acetate) and recrystallization in hexane gave 0.67 g (70%) of major diastereomer (*S*,*R*)-**9b**, and 0.14 g (15%) of minor diastereomer (*R*,*R*)-**9b**.

(2*S*,4*R*)-*N*-Benzoyl-2-difluoromethyl-2-methyl-4-phenyl-1,3-oxazolidine (*S*,*R*)-9b: white solid; mp 75−76 °C; $[\alpha]^{20}_D$ −211.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.93 (dd, 1H, $^2J_{HH}$ = 8.5, $^3J_{HH}$ = 1.2), 4.53 (dd, 1H, $^2J_{HH}$ = 8.5, $^3J_{HH}$ = 7.0), 4.87 (dd, 1H, $^3J_{HH}$ = 7.0, 1.2), 6.48 (t, 1H, $^2J_{HF}$ = 56.5), 6.7−7.6 (m, 8H), 8.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.8, 62.9, 74.1, 94.6 (dd, $^2J_{CF}$ = 22.0, 19.3), 113.7 (t, J_{CF} = 248.0), 125.8, 126.4, 128.1, 128.4, 128.6, 130.1, 136.6, 140.5, 170.3; ^{19}F NMR ($CDCl_3$) δ −134.2 (dd, 1F, $^2J_{FF}$ = 280.9, $^2J_{HF}$ = 56.5), −137.1 (dd, 1F, $^2J_{FF}$ = 280.9, $^2J_{HF}$ = 56.5); IR (KBr) ν 3087, 3007, 2912, 1635, 1577, 1394, 1252, 1062; HRMS calcd for $C_{18}H_{17}F_2NO_2$ (M + 1) 318.1309, found 318.1306.

(2*R*,4*R*)-*N*-Benzoyl-2-difluoromethyl-2-methyl-4-phenyl-1,3-oxazolidine (*R*,*R*)-9b: white solid; mp 105−107 °C; $[\alpha]^{20}_D$ −187.1 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.86 (s, 3H), 4.19 (t, 1H, $^2J_{HH}$ = $^3J_{HH}$ = 8.3), 4.42 (t, 1H, $^2J_{HH}$ = $^3J_{HH}$ = 8.3), 5.01 (t, 1H, $^3J_{HH}$ = 8.3), 6.78 (t, 1H, $^2J_{HF}$ = 55.6), 6.9−7.6 (m, 8H), 8.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.4, 63.1, 74.9, 95.1 (t, $^2J_{CF}$ = 2.7), 114.7 (t, J_{CF} = 248.7), 126.0, 127.2, 127.9, 128.3, 128.4, 130.1, 136.7,

(23) Bravo, P.; Capelli, S.; Meille, S. V.; Seresini, P.; Volontario, A.; Zanda, M. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2321−2332.

137.9, 170.2; ^{19}F NMR ($CDCl_3$) δ −131.8 (dd, 1F, $^2J_{FF}$ = 281.8, $^2J_{HF}$ = 55.6), −132.1 (dd, 1F, $^2J_{FF}$ = 281.8, $^2J_{HF}$ = 55.6).

General Procedure for the Reduction of 1,3-Oxazolidines with LAH. To a solution of oxazolidine (1.0 mmol) in 40 mL of diethyl Et_2O at room temperature under argon was added LAH (1.2 mmol, 1.2 equiv). After being stirred for 24 h, the reaction mixture was successively treated with water (0.2 mL), 15% aq KOH (0.2 mL), and water (4 mL). The resulting mixture was filtered on Celite, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. This procedure afforded the corresponding amines **10a** and **13b** (see the Supporting Information). A shorter reaction time allowed us to isolate the *N*-benzyloxazolidine (*R*,*R*)-**14**.

Preparation of Enantiopure α-Difluoromethylamine. To a solution of compound (*R*,*R*)-**10a** (0.27 g, 0.96 mmol) in MeOH/CH_2Cl_2 2:1 (10 mL) was added at 0 °C $Pb(OAc)_4$ (620 mg, 1.4 mmol, 1.4 equiv). After 20 min of stirring at 0 °C, the reaction mixture was poured into a phosphate buffer aqueous solution pH = 7 (10 mL) at room temperature and then filtered over Celite. The aqueous phase was extracted with dichloromethane (4 × 10 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford quantitatively (*R*)-**11a** as a yellow oil. A similar procedure applied to (*S*,*R*)-**10a** gave (*S*)-**11a.** The imine (*R*)-**11a** was stirred for 24 h in a 1:1 mixture of 3 M HCl/ Et_2O (5 mL). The aqueous phase was extracted with Et_2O and concentrated under reduced pressure to afford (*R*)-(−)-**12a** (0.15 g, 80%, two steps from (*R*,*R*)-**10a**) as a white powder which decomposed on heating. Similarly, (*S*)-(+)-**12a (**0.14 g, 73%, two steps) was prepared from (*S*)-**11a**.

(*R*)-(−)-2,2-Difluoro-1-phenylethylamine hydrochloride (*R*)-(−)-12a: $[\alpha]^{20}_D$ −17.0 (*c* 0.2, H_2O); ^{1}H NMR (D_2O) δ 4.8 (m, 1H), 6.22 (ddd, 1H, $^2J_{HF}$ = 53.9, 52.9, $^3J_{HH}$ = 2.8), 7.37 (m, 5H); ^{13}C NMR (D_2O) δ 56.2 (dd, $^2J_{CF}$ = 23.8, 21.2), 114.2 (t, J_{CF} = 245.7), 128.5, 129.9, 130.9, 138.1; ^{19}F NMR (D_2O) δ −123.3 (ddd, 1F, $^2J_{FF}$ = 285.4, $^2J_{HF}$ = 52.9, $^3J_{HF}$ = 9.0), −130.5 (ddd, 1F, $^2J_{FF}$ = 285.4, $^2J_{HF}$ = 53.9, $^3J_{HF}$ = 8.0).

(*S*)-(+)-2,2-Difluoro-1-phenylethylamine hydrochloride (*S*)-(+)-12a: $[\alpha]^{20}_D$ +18.0 (*c* 2.3, H_2O).

(*R*)-(+)-1-Difluoromethylethylamine Hydrochloride (*R*)-(+)-12b. To a stirred solution of diastereomer (*R*,*R*)-**13b** (0.31 g, 1.0 mmol) in 5 mL of methanol was added in one portion 0.50 g of Perlman catalyst (0.5 mmol, 0.02 equiv). The reaction mixture was stirred under H_2 atmosphere until complete consumption of starting material (TLC). After filtration on Celite, the filtrate was diluted with a 1:1 mixture of HCl (3 N)/Et_2O. After 2 h of stirring, the aqueous phase was extracted with Et_2O and concentrated under reduced pressure to afford 57 mg of (*R*)-(+)-**12b** (35%) as a white powder which decomposed on heating: $[\alpha]^{20}_D$ +5.4 (*c* 0.4, H_2O); ^{1}H NMR (D_2O) δ 1.36 (d, 3H, $^3J_{HH}$ = 6.9), 3.77 (dddq, 1H, $^3J_{HF}$ = 18.8, 8.1, $^3J_{HH}$ = 6.9, 2.0), 6.10 (td, 1H, $^2J_{HF}$ = 53.9, $^3J_{HH}$ = 2.0); ^{13}C NMR (D_2O) δ 11.9 (dd, $^3J_{CF}$ = 5.5, 2.8), 48.9 (t, $^2J_{CF}$ = 22.1), 114.7 (t, J_{CF} = 243.1); ^{19}F NMR (D_2O) δ −125.7 (ddd, 1F, $^2J_{FF}$ = 286.3, $^2J_{HF}$ = 53.9, $^3J_{HF}$ = 8.1), −133.8 (ddd, 1F, $^2J_{FF}$ = 286.3, $^2J_{HF}$ = 53.9, $^3J_{HF}$ = 18.8).

Preparation of Enantiopure α-Difluoromethyl-α-amino Acids. To a solution of oxazolidines **6b** (0.54 g, 2.5 mmol) in CH_2Cl_2 (20 mL) under argon at 0 °C were successively added TMSCN (2.76 mL, 3.75 mmol, 1.5 equiv) and BF_3·OEt_2 (2.6 mL, 3.75 mmol, 1.5 equiv). The temperature was slowly raised to room temperature, and after conversion of the starting material (TLC), the reaction mixture was poured into a saturated aq $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The two diastereomers were separated by flash chromatography (4:1 petroleum ether/ ethyl acetate), giving (*R*,*R*)-**15b** (yellow oil, 0.24 g, 40%) and (*S*,*R*)-**15b** (solid, 0.18 g, 30%). The same procedure was applied to **6a** (0.28 g, 1.0 mmol) to give a major (145 mg, 48%) and a minor (115 mg, 38%) diastereomer of propionitrile **15a** (SI) as yellow oils.

(*R*,*R*)-**15b** (0.24 g, 1.0 mmol) was treated with $Pb(OAc)_4$ as described for **10a** to afford (*R*)-**16** as a pale yellow oil. A solution of (*R*)-**16** (0.21 g, 1.0 mmol) in 6 M aq HCl (5 mL) was heated at reflux for 14 h. After cooling to rt and treatment with Et_2O (5 mL), concentration of the aqueous phase afforded the amino acid hydrochloride (*R*)-(+)-**17** (147 mg, 84%) as a white powder. This solid was dissolved in propylene oxide (10 mL) and stirred for 24 h at room temperature. The crude mixture was concentrated under reduced pressure. Pure (*R*)-(+)-**18** (72 mg, 62%) was obtained after crystallization in methanol.

(*R*)-(+)-2-Difluoromethylalanine (*R*)-18:[23] white solid; mp = 194 °C dec (lit.[23] 196 °C); $[\alpha]^{20}_D$ +14.70 (*c* 0.60, H_2O) (lit.[23] $[\alpha]^{20}_D$ +15.35 (*c* 0.85, H_2O)); ^{1}H NMR (CD_3OD) δ 1.51 (s, 3H), 6.19 (t, 1H, $^2J_{HF}$ = 53.1); ^{13}C NMR (CD_3OD) δ 20.0 (t, $^3J_{CF}$ = 43.8, 64.4 (t, $^2J_{CF}$ = 19.7), 118.4 (t, J_{CF} = 246.5), 175.0; ^{19}F NMR (CD_3OD) δ −126.2 (dd, 1F, $^2J_{FF}$ = 275.6, $^2J_{HF}$ = 53.1), −132.0 (dd, 1F, $^2J_{FF}$ = 275.6, $^2J_{HF}$ = 53.1).

Similar successive treatments were applied to (*S*,*R*)-**15b** (0.24 g, 1.0 mmol) to afford (*S*)-**16** (pale yellow oil), then (*S*)-(−)-**17** (136 mg, 78%) (white powder), and finally (*S*)-**18**.

(*S*)-(−)-2-Difluoromethylalanine (*S*)-18: $[\alpha]^{20}_D$ −15.0 (*c* 0.40, H_2O).

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Supporting Information Available: Complementary procedures and data of the compounds **3a**,**b**, **4a**,**b**, **7**, **8**, **6b**, (*R*,*R*)-**14**, (*R*,*R*)-**10a**, (*S*,*R*)-**10a**, **12b**, (*S*,*R*)-**13b**, (*R*,*R*)-**13b**, (*R*)-**11a**, (*S*)-**11a**, **15a**, (*R*,*R*)-**15b**, (*S*,*R*)-**15b**, (*R*)-**16**, (*S*)-**16**, (*R*)-**17**, (*S*)-**17**. ^{1}H, ^{19}F, and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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